

# PSA Evaluation Methodologies: New Alternatives

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*Abstract*

In this paper we develop a maximum likelihood method to discriminate between benign prostates, PCa, PIN and BPH using data collected over long time horizons and using a systems model of prostate cell growth and PSA generation by cell type. The model allows for a sequential analysis over the long time horizon and it demonstrates the use of secondary data such as age, family history and race as well.

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## 1 INTRODUCTION

Currently there are a few readily measurable factors which we can ascertain whether a patient has PCa or not. The use of PSA, PSA velocity and % Free PSA are three measures we often see used and when used they result in considerable debate. One of the issues is that the gold standard test, namely biopsy of the prostate, itself has substantial error in determining if PCa exists. The only true standard currently available is biopsy of the removed prostate. The latter gold standard is hardly one useful in clinical studies of patients with no overt signs upon normal evaluation.

We thus are looking at other measures for ascertaining patient status regarding the PCa presence. Clearly if we had a better understanding of cellular pathways and if in so understanding there were more useful markers which could be readily available, then perhaps we could have a more robust set of tests. However, lacking such, we are left with the three measures and other exogenous variable such as age, family history, race. In this paper we use these factors as a means to ascertain the efficacy of various approaches to determining if the patient has PCa. This is not a staging approach, it is merely a monitoring effort, a screening effort, which could be used assuming that long term consistent data is available. The latter point is often a handicap since the assays used over some period of time are often highly variable in their results. We model this with a noisy measurement variable.

We thus analyze several various approaches with a primary focus on a systems approach. The systems approach is consistent with the Dougherty dictates which we try to adhere to, with predictability and reproducibility being the dominant ones. The system model we develop herein is a simple model based upon measurable parameters which can be validated by its predictable capacity. The approach is to view the resulting data such as PSA over time to be capable of providing, along with other data, more reliable metrics for assessing the potential for PCa.

The key risk in such a model is the ability to use measurable parameters across some wide base of patients. There is not reliable answer to this at the current time. Perhaps this is just a problem of “kicking the ball down the street” with solving one part of the problem by merely placing the uncertainty on another portion.

## 2 THE PROBLEM

We present a simple model of the problem herein. We look at the study but Punglia et al as a baseline upon which to understand the issue. We also look at the analysis we have performed regarding the probability of missing a PCa on a biopsy, which is not inconsequential.

Let us look at a simple version of Punglia model. We show this below:

	Test Positive	Test Negative	
Disease Positive	100	50	150
Disease Negative	50	250	300
	150	300	450

This simple model then gives the probabilities of Sensitivity as 100/150 and Specificity of 250/300. However we know that if there were a PCa, then depending on its size we would expect a P[Missing PCa] of 25% or somewhere in that range. The question then is how does one modify this Table to account for that. Punglia modifies it for verification bias, namely just filling in those who were tested but not biopsied in some rational manner. Punglia alleges used data predicated on patient statistics. The approach was unfortunately not detailed in the paper. We performed another analysis wherein we looked at using the Zhou analysis based on Begg and Greenes approach. The answers were dramatically different.

Now using the above we get a Sensitivity of 66% and a Specificity of 83%. But let us make a simple set of assumptions for this case. We will arbitrarily assume that the miss rate in the case where there is PCa is 40% and where there is “no PCa” say 10%. The Table changes as follows:

	Test Positive	Test Negative	
Disease Positive	130	20	150
Disease Negative	75	225	300
	205	245	450

Then we have:

$$\text{Sensitivity} = 130/150 = 87\%$$

$$\text{Specificity} = 225/300 = 75\%$$

	Punglia	Adjusted
Sensitivity	66%	87%
Specificity	83%	75%

This is a non-trivial difference. The test becomes much more sensitive. It loses some specificity but it more than makes up for sensitivity. Thus is if we were to place costs on a test and its follow up, the higher the sensitivity the better it is since we then end up treating the disease. Thus there is a need to better adjust the tests accordingly.

There are two fold elements in adjusting tests. First we desire a better test using PSA and its adjuncts. Second, we need a better way to assess the gold standard, and if no possible then adjust the data to reflect the known lack of accuracy as we have shown here.

### 3 ALTERNATIVES

There are many ways in which one may use the available data and then use it to ascertain the presence or absence of PCa. None have superb diagnostic characteristics as far as detections systems go. However we look at two classic approaches herein and we first introduce the systems model which we have not observed in any of the current literature. The three approaches are:

**Systems Model:** This is a model which looks at cell growth and the resulting markers that such cells produce. We can measure the markers such as PSA and we can ascertain experimentally all of the parameters in the model. As we have stated before, the risk is that the parameters in the model have so great a patient to patient variability that the ultimate model is of little use. However there is not adequate data at this time to make that judgment.

#### 3.1 The System Approach

The systems model looks directly at the cell growth and the resulting process within cells to emit PSA into the blood stream for monitoring. We use a simple birth-death model as a first approximation for cell size.

##### 3.1.1 Basic Systems Model

Let assume we have a certain number of benign prostate cells. For the purpose of further simplicity we shall focus on luminal and basal cells and for the further purpose we shall use a Goldstein model and assume that luminal are derived from basal and thus can be considered as one type. Thus we assume the prostate a simply an organized collection of a single set of benign cells. Then we have:

$$\frac{dN_{Benign}(t)}{dt} = \lambda_{Benign}N_{Benign}(t) - \mu_{Benign}N_{Benign}(t)$$

$\lambda$  = Birth Rate

$\mu$  = Death Rate

$N$  = Number of cells

Now if the cells are stable then we have birth and death rates equal. Death in this cases is by normal apoptosis and birth is mitosis. We must recall that even in mitotic growth

the apoptotic process is such as to keep total cell numbers at constant levels. This in benign conditions we have:

$$N_{Benign}(t) = N_B(t) = N_B(t_0)$$

Now let us consider an amalgam of the following types of cells:

1. Benign
2. Cancer
3. PIN
4. BPH

Each has its own growth characteristics. Each has its own birth-death equations, measurable in vitro for example. Yet they may actually interact. For example PCa cells may cause increased apoptosis amongst Benign cells, pushing them aside for their own benefit. BPH may grow on top of normal cells, for in fact they are a basic extension thereto. PIN may also extend on top of Benign cells but just enlarging the prostate as would be seen with BPH but with cells confined to the glands but with differing characteristics. Thus we seek to have models which combine all. Birth and death rates may be dependent in some general way on each other. Thus we could in general posit:

$$\frac{dN_i(t)}{dt} = \left[ \sum_{n=1}^6 \lambda_n(N_1, \dots, N_6) - \mu_i(N_1, \dots, N_6) \right] N_i(t) + w_i(t)$$

where

$$N_1 = \text{Benign}$$

$$N_2 = \text{PCa}$$

$$N_3 = \text{PIN}$$

$$N_4 = \text{BPH}$$

Here we have added a random process,  $w$ , which we shall assume is Gaussian Wiener process with zero mean and some determinable variance. The birth and death rates are determinable via experimental analyses.

We shall consider some simple binary models for this analysis.

Now we also note that we can relate PSA and % Free PSA ("PFP") as functions of  $N$ , the number of specific cells. Let us consider this as follows:



$$PSA(t) = \sum_{n=1}^6 psa_n N_n(t)$$

where

$psa_n$  = the PSA per cell of type  $n$  in circulation

and

$$PPP(t) = \sum_{n=1}^6 pfp_n N_n(t)$$

where

$pfp_n$  = the PFP per cell of type  $n$  in circulation

Thus we measure PSA(t) and PFP(t) over some set of time intervals. A simple thought experiments indicates that we can see stable PSA and PFP if we have benign cells, subject to normal noise which we have included.

Let us now consider two cases.

Case I: Benign and PIN. Here we assume benign and PIN. The PIN is additional cell growth but not as extensive as say BPH. We have the following model:

$$\frac{dN_B(t)}{dt} = [\lambda_B - \mu_B] N_B(t) + w_B(t)$$

$$\frac{dN_{PIN}(t)}{dt} = [\lambda_{PIN} - \mu_{PIN}] N_{PIN}(t) + w_{PIN}(t)$$

where

$$\lambda_B - \mu_B = 0$$

$$\lambda_{PIN} - \mu_{PIN} > 0$$

Note that we stable Benign calls but a slowly growing PIN set of cells. And this yields for the exogenous measurements the following:

$$PSA(t) = psa_B N_B(t) + psa_{PIN} N_{PIN}(t)$$

and

$$PFP(t) = \frac{pfp_B N_B(t) + pfp_{PIN} N_{PIN}(t)}{N_B(t) + N_{PIN}(t)}$$

Now as we see more PIN cells we see a slowly increasing PSA, subject to noise, and we see a PPT also changing on a weighted basis. Yet if pfb is identical for both Benign and PIN then we see that PFP remains constant and high.

Case II: PCa: In this case we have benign and cancer cells. The same model as above but with some substantial modifications. We see this first as follows:

$$\frac{dN_B(t)}{dt} = [\lambda_B - \mu_B(N_{PCa}(t))]N_B(t) + w_B(t)$$

$$\frac{dN_{PCa}(t)}{dt} = [\lambda_{PCa} - \mu_{PCa}]N_{PCa}(t) + w_{PCa}(t)$$

where

$$\lambda_B - \mu_B > 0$$

$$\lambda_{PCa} - \mu_{PCa} \gg 0$$

and

$$\frac{\partial \mu_B}{\partial N_{PCa}} > 0$$

This implies that we have a decreasing cell count of benign cells and an increasing and growing count of PCa cells. Thus when we calculate the following:

$$PSA(t) = psa_B N_B(t) + psa_{PCa} N_{PCa}(t)$$

and

$$PFP(t) = \frac{pfp_B N_B(t) + pfp_{PCa} N_{PCa}(t)}{N_B(t) + N_{PCa}(t)}$$

We see that the number of PCa cells are growing and at a rate in excess of and Benign cells, which are declining and that psa of PCa is much smaller than that of Benign cells as it the pfp of PCa, which is quite small as compared to benign cells. Thus with PCa we see PSA increasing and PFP decreasing.

Now the question we pose is how do we determine:

$$P[PCa | PSA(s), PFP(s); s \in (t_0, t)]$$

This is a classic detection problem. We have solved that problem in our earlier work<sup>1</sup>. We will present the analytical approach here. Before continuing, however, we want to demonstrate what we know and what we have speculated:

We know the following from experiment and can validate from more experiments:

1. Cell growth follows the models we have depicted.

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<sup>1</sup> See McGarty, *Stochastic Systems and State Estimation*, Wiley, 1974.

2. Growth rates are determinable from such factors as mitotic rates and other methods which are well known.
3. Cancer cells do push our benign cells through a variety of methods which are well understood.
4. The measurements we have determined are well documented and the average rates we use in the models are determinable from measurements.

We do not really know the following:

1. The functional characteristic of the increased death rate, and even birth rate, of benign cells dependent on the new PCa cells. There is the issue of the PCa cells absorbing nutrients from the Benign cells as well as the issue of reducing normal mitotic reactions.

### 3.1.2 Hypothesis Detection Model

The detection model can be defined as follows:

#### Hypothesis 0: Benign

$$PSA(t) = psa_B N_B(t)$$

and

$$PFP(t) = \frac{pfp_B N_B(t)}{N_B(t)}$$

And

$$\frac{dN_B(t)}{dt} = [\lambda_B - \mu_B] N_B(t) + w_B(t)$$

where

$$\lambda_B - \mu_B = 0$$

#### Hypothesis 1: PCa

$$PSA(t) = psa_B N_B(t) + psa_{PCa} N_{PCa}(t)$$

and

$$PFP(t) = \frac{pfp_B N_B(t) + pfp_{PCa} N_{PCa}(t)}{N_B(t) + N_{PCa}(t)}$$

and

$$\frac{dN_B(t)}{dt} = [\lambda_B - \mu_B(N_{PCa}(t))]N_B(t) + w_B(t)$$

$$\frac{dN_{PCa}(t)}{dt} = [\lambda_{PCa} - \mu_{PCa}]N_{PCa}(t) + w_{PCa}(t)$$

where

$$\lambda_B - \mu_B > 0$$

$$\lambda_{PCa} - \mu_{PCa} \gg 0$$

and

$$\frac{\partial \mu_B}{\partial N_{PCa}} > 0$$

Thus we want to find a detector, maximum likelihood as an example, using:

$$P[PCa|DataSet] = \frac{P[DataSet|PCa]P[PCa]}{P[DataSet]}$$

### 3.1.3 Adequacy of Data in Model

We now take a brief look at what the effects of patient to patient variability would be in the model. As we said, there are measurable constants which we can ascertain and use in the model. There are two sets of the constants. The first set if the growth parameters and the second is the measurement parameters.

Let us consider the growth first. We assume that there is an average parameter and some variation about that average. We then ask how do we modify the model accordingly. This is a simple first order modification where the  $\delta$  represent the zero mean variation of the measurement of the related variable with a variance  $\sigma$  associated with it as determined from the measurement data. Thus we have:

$$\frac{dN_B(t)}{dt} = [\hat{\lambda}_B + \delta\lambda_B - \hat{\mu}_B + \delta\mu_B]N_B(t) + w_B(t)$$

$$= [\hat{\lambda}_B - \hat{\mu}_B]N_B(t) + [\delta\lambda_B + \delta\mu_B]N_B(t) + w(t)$$

$$= [\hat{\lambda}_B - \hat{\mu}_B]N_B(t) + u(t) + w(t)$$

where

$$\lambda_B - \mu_B = 0$$

This model then uses the uncertainty of the measurements as an added noise term, albeit correlated with the cell count. If the “noise” associated with the measurements is

small with respect to the count itself then we can reasonably augment the overall system noise to include that level.

This is a first order approach to including the issue of measurement uncertainty of the underlying parameters.

We can do the same with the measurements:

$$\begin{aligned} PSA(t) &= ps_{a_B} N_B(t) + ps_{a_{PCa}} N_{PCa}(t) \\ &= (ps_{\hat{a}_B}) N_B(t) + ps_{\hat{a}_{PCa}} N_{PCa}(t) + \delta ps_{a_B} N_B(t) + \delta ps_{a_{PCa}} N_{PCa}(t) \\ &= (ps_{\hat{a}_B}) N_B(t) + ps_{\hat{a}_{PCa}} N_{PCa}(t) + r(t) \end{aligned}$$

Where we replace the uncertainty with an  $r(t)$  as we did above.

### 3.2 Logistic Analyses

The logistic approach looks at the probability of PCa and its dependence on certain variables. For the purpose of this analysis we know that it depends on:

1. PSA Level
2. % Free PSA
3. Velocity of PSA
4. Age
5. First Degree Relatives Having PCa
6. Race

This in a simple logistic model we define:

$$\ln \left[ \frac{P[PCa]}{1 - P[PCa]} \right] = \alpha + \sum_{n=1}^6 \beta_n x_n$$

where

$x_1 = PSA \text{ level}$

$x_2 = \% \text{ Free PSA}$

$x_3 = PSA \text{ velocity}$

$x_4 = \text{Age}$

$x_5 = \text{First Degree Relatives}$

$x_6 = \text{Race}$

As compared to the system model which is based upon verifiable constants and an clear underlying physical process and model, this is pure statistical conjecture. Here we will use volumes of data to attempt to ascertain the relationships. In logistic analysis the relationship is posited ab initio and there may or may not be any underlying physical relationship. We merely use the data and then from the data try to fit the constants based upon a clinical determination of the disease state.

### 3.3 Classification Methodologies

Classification approaches include such methods as clustering, principal component analyses, and other such methods. If we have say six measurables at our hand then we can collect a great deal of data with an assumed determination of PCa being absent or present. Then in this six dimensional space we can map out sectors which show how we could split the space into PCa and Benign space. We leave it to the reader to see the use of these techniques and refer them to the references at the end of this paper. As Dougherty so aptly states, the use of many classifiers are based solely upon the data and its characteristics and it devoid of any understanding of the inherent pathology.

## 4 A MAXIMUM LIKELIHOOD SYSTEMS CLASSIFIER

We can now use the systems model to develop a classifier. We start with a simple binary decision between two hypotheses; benign or PCa. We assume that the system can be delivered in a discrete time manner, which frankly we know. We will follow the approach in VanTrees for this analysis. Thus we have for the system:

$$N_B(k+1) = N_B(k) + (\lambda_B(k) - \mu_B(k))N_B(k) + w_B(k)$$

*under  $H_0$  which is the hypothesis of benign*

*and under this hypothesis we have*

$$N(k) = N_B(k)$$

$$N_B(k+1) = N_B(k) + (\lambda_B(k) - \mu_B(k))N_B(k) + w_B(k)$$

$$N_{PCa}(k+1) = N_{PCa}(k) + (\lambda_{PCa}(k) - \mu_{PCa}(k))N_{PCa}(k) + w_{PCa}(k)$$

*under  $H_1$  which is the hypothesis of PCa*

*and under  $H_1$  we have*

$$N(k) = N_B(k) + N_{PCa}(k)$$

This is a model for a Markov process assuming the noise is independent and Gaussian and it has zero mean. The variance may be time or sample dependent. Note also that we may have to adjust the birth and death constants to reflect the time between samples.

Now what we measure is:

Under  $H_0$  we have:

$$PSA(k) = psa_B N_B(k) + n_{PSA,B}(k)$$

and

$$PFP(k) = \frac{pfp_B N_B(k)}{N_B(k)} = pfb_B N_B(k) + n_{PFP,B}(k)$$

Under  $H_1$  we have:

$$PSA(k) = psa_B N_B(k) + psa_{PCa} N_{PCa}(k) + n_{PSA,Both}(k)$$

and

$$PFP(k) = \frac{pfp_B N_B(k) + pfp_{PCa} N_{PCa}(k)}{N_B(k) + N_{PCa}(k)} + n_{PFP,Both}(k)$$

Here the  $n(k)$  is a measurement noise sequence reflecting both assay errors as well as variations from the base line estimates. What we use for the decision statistics are the above sets of variables. The difficulty would be that they are derived from the same data sequences, the  $N(k)$  sequences and thus are combinations of variables. Also we can simplify the PFP by normalizing it by volume, assuming that the cells are each of equal volume. Namely benign cells and PCa cell have essentially the same volume. Thus we can write the above measurements as a simplified linear model as follows:

Under  $H_0$  we have:

$$PSA(k) = psa_B N_B(k) + n_{PSA,B}(k)$$

and

$$PFP(k) = pfb_B N_B(k) + n_{PFP,B}(k)$$

Under  $H_1$  we have:

$$PSA(k) = psa_B N_B(k) + psa_{PCa} N_{PCa}(k) + n_{PSA,Both}(k)$$

and

$$PFP(k) = pfp_B N_B(k) + pfp_{PCa} N_{PCa}(k) + n_{PFP,Both}(k)$$

Where we use volumetric normalized values for PFP.

Now we want the probabilities of PSA and PFP for all ks. We can write<sup>2</sup>:

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<sup>2</sup> Note we use the notation  $N(a,b)$  as a normal or Gaussian distribution with mean  $a$  and standard deviation  $b$ .

For  $H_0$

$$p(PSA(k), PFP(k) | N(k)) = \tilde{N}(psaN(k), \sigma_{PSA}) \tilde{N}(pfpN(k), \sigma_{PFP})$$

and

$$p(PSA(k), PFP(k), N(k) | N(k-1)) = \tilde{N}(psaN(k), \sigma_{PSA}) \tilde{N}(pfpN(k), \sigma_{PFP}) \tilde{N}((\lambda - \mu)N(k-1), \sigma_N(k))$$

Thus we have the joint conditional probability being all Gaussian with known means and we know that the  $N(k)$ s are themselves incrementally conditionally independent since we have a Wiener process and it is independent.

Now if we use the likelihood ratio we want the following:

Let

$$r_{PSA} = \begin{bmatrix} PSA(1) \\ \dots \\ PSA(n) \end{bmatrix}$$

$$r_{PFP} = \begin{bmatrix} PFP(1) \\ \dots \\ PFP(n) \end{bmatrix}$$

$$r = \begin{bmatrix} r_{PSA} \\ r_{PFP} \end{bmatrix}$$

These represent the received vectors. To define the likelihood ratios we then use these:

$$p(r | H_0) = \int p(r | x, H_0) p(x | H_0) dx$$

But

$$p(r | x, H_0) = \prod_{n=1}^N p(r_n | x_n, H_0)$$

and

$$p(x | H_0) = \prod_{n=1}^N p(x_n | x_{n-1}, H_0)$$

And they are all normal with defined means and variances. We thus can pairwise deal with these. However the inclusion of noise on the cell count model adds a bit of complexity so we shall assume that it can be ignore in a first order approximation. Then we can easily determine the likelihood ratio parameters as follows:



For  $H_0$

$$N_B(k+1) = N_B(k) + (\lambda - \mu)N_B(k)$$

and for non-uniform intervals we write:

$$N_B(k+1) = N_B(k) + (\lambda - \mu)\Delta(k)N_B(k)$$

where we have  $\lambda$  and  $\mu$  normalized accordingly

$\Delta(k)$  then is the sample time difference

For the measurements we have:

$$PSA(k) = psa_B N_B(k) + n_{PSA,B}(k)$$

and

$$PFP(k) = pfp_B N_B(k) + n_{PFP,B}(k)$$

These are independent random variables driven by the underlying count. Note that the sampling time issues plays no part in this expression. Obviously we have the same for the other case of PCa.

It can easily be shown that the likelihood ratio, specifically the log likelihood ratio can be given as follows:

Choose  $H_0$  if:

$$\sum_{n=1}^N [PSA(k) - psa_B \alpha_B \Delta(n) N_0]^2 + [PFP(k) - pfp_B \alpha_B \Delta(n) N_0]^2 >$$

$$\sum_{n=1}^N \frac{[PSA(k) - psa_B \alpha_{B,PCa} \Delta(n) N_0 - psa_{PCa} \alpha_{PCa} \Delta(n) N_0^{PCa}]^2}{\sigma_{PSA}^2}$$

$$+ \frac{[PFP(k) - pfp_B \alpha_{B,PCa} \Delta(n) N_0 - pfp_{PCa} \alpha_{PCa} \Delta(n) N_0^{PCa}]^2}{\sigma_{PFP}^2}$$

Now we can consider the issue of choosing between the four hypotheses; B, PIN, BPH, and PCa. Again we rely upon the treatment in VanTrees. The model follows directly from above.

Let the following be the hypotheses:

$$H_0 = \text{Benign}$$

$$H_1 = \text{BPH}$$

$$H_2 = \text{PIN}$$

$$H_3 = \text{PCa}$$

Then we create the following likelihood ratios:

$$\Lambda_{i,j}(r) = \frac{p(r|H_i)}{p(r|H_j)}$$

Then we can set up the decision regions based upon the following rules:

$$\Lambda_{0,1}(r) \begin{cases} < c_{0,1} : \text{Choose } H_0 \text{ or } H_2 \text{ or } H_3 \\ > c_{0,1} : \text{Choose } H_1 \text{ or } H_2 \text{ or } H_3 \end{cases}$$

$$\Lambda_{1,2}(r) \begin{cases} < c_{1,2} : \text{Choose } H_1 \text{ or } H_0 \text{ or } H_3 \\ > c_{1,2} : \text{Choose } H_2 \text{ or } H_0 \text{ or } H_3 \end{cases}$$

$$\Lambda_{2,3}(r) \begin{cases} < c_{2,3} : \text{Choose } H_2 \text{ or } H_0 \text{ or } H_1 \\ > c_{2,1} : \text{Choose } H_3 \text{ or } H_0 \text{ or } H_1 \end{cases}$$

$$\Lambda_{0,2}(r) \begin{cases} < c_{0,2} : \text{Choose } H_0 \text{ or } H_1 \text{ or } H_3 \\ > c_{0,2} : \text{Choose } H_2 \text{ or } H_1 \text{ or } H_3 \end{cases}$$

$$\Lambda_{0,3}(r) \begin{cases} < c_{0,3} : \text{Choose } H_0 \text{ or } H_1 \text{ or } H_2 \\ > c_{0,3} : \text{Choose } H_3 \text{ or } H_1 \text{ or } H_2 \end{cases}$$

$$\Lambda_{1,3}(r) \begin{cases} < c_{1,3} : \text{Choose } H_1 \text{ or } H_0 \text{ or } H_2 \\ > c_{1,3} : \text{Choose } H_3 \text{ or } H_0 \text{ or } H_2 \end{cases}$$

These then set out mutually exclusive decision regions. The details are in VanTrees. Generally we seek a binary decision between something and PCa. Knowing these regions we can quantitatively calculate the ROC related probabilities and we can choose the thresholds to maximize the ROC areas as has been suggested in the literature.

## 5 EXAMPLE

We now consider a simple example. This is one where we are looking at almost 20 years of data, some missing, and we then look at a binary hypothesis of B or PIN. Consider the data on the following patient:

Year	PSA(Alone)	Delta PSA	Delta/Yr PSA Abs	PSA Velocity 3- SampleTests	PSA Free	PSA on Free PSA	%Free PSA
Feb-93	0.62	-	-	-	-	-	-
Mar-94	0.53	(0.15)	(0.09)	-	-	-	-
Feb-95	1.50	1.76	1.01	-	-	-	-
Jan-96	0.62	(0.53)	(0.98)	(0.02)	-	-	-
Jan-97	0.70	0.13	0.08	0.04	-	-	-
Apr-98	0.77	0.12	0.06	(0.28)	-	-	-
Aug-99	0.95	0.31	0.14	0.09	-	-	-
Jul-00	1.10	0.14	0.16	0.12	-	-	-
Aug-00	1.10	-	-	0.10	-	-	-
Oct-01	1.10	-	-	0.05	-	-	-
Nov-02	1.30	0.19	0.19	0.06	-	-	-
Nov-03	1.19	(0.08)	(0.11)	0.03	0.50	1.30	38%
Nov-04	1.53	0.30	0.32	0.13	0.50	1.53	33%
Nov-05	1.22	(0.19)	(0.33)	(0.04)	0.50	1.53	33%
Dec-06	1.60	0.35	0.34	0.11	0.50	1.53	33%
Nov-07	1.49	(0.06)	(0.12)	(0.04)	0.50	1.53	33%
Nov-08	1.49	-	-	0.07	-	-	-
Nov-09	2.20	0.48	0.70	0.19	-	-	-
Feb-10	2.10	(0.01)	(0.52)	0.06	0.70	1.53	33%
Feb-10	1.80	(0.00)	(2.03)	(0.62)	0.70	1.53	39%
May-10	1.70	(0.01)	(1.57)	(1.37)	0.70	1.53	39%
Oct-10	2.00	0.08	0.27	(1.11)	-	-	-

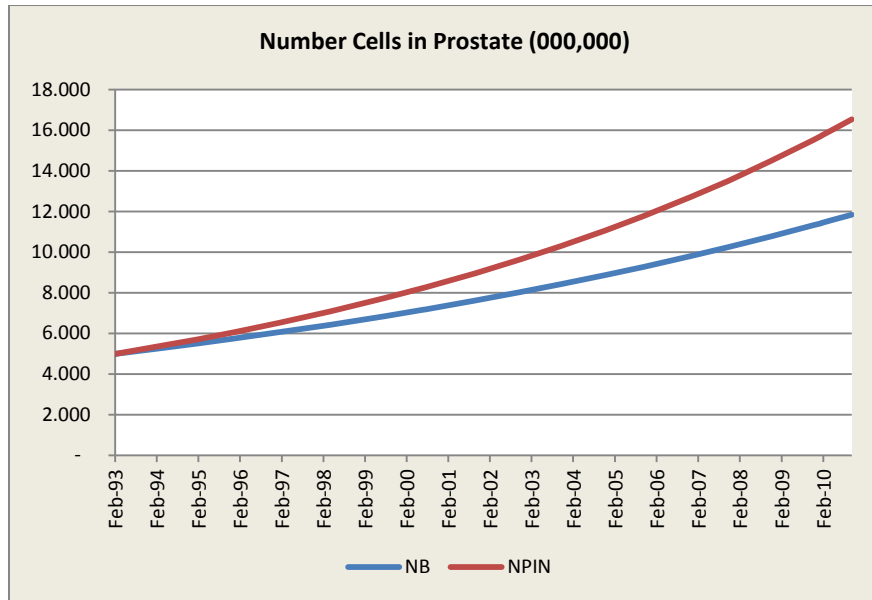
We now use the test we had above. We must look at the underlying statistics.

1. Variance of both PSA and PFP are about a 25% standard deviation. Thus since both are the same these factors can be removed from the analysis.
2. The number of normal cells in a 40 cc prostate can be assumed to be 10 million. We assume that we can normalize cell numbers in millions so that a cell count of 10 is the equivalent of 10 million.
3. We can assume that a benign prostate of 40 cc has a base level in a 40 year old male is 0.5 and PFP is 35%.
4. We can further assume that we have in a normal prostate a 25% increase in size per decade as the man ages over 50. Thus there is a 25% change. In contrast with BPH the doubling is every 5 years and for PIN we have every 7.5.
5. We assume that both BPH and PIN cells secrete the same PSA and the binding is the same.
6. We assume that the doubling rate for cells with PCa is much shorter, namely 3 months and that PSA is the same per cell but PFP is 5% per cell not 35%.

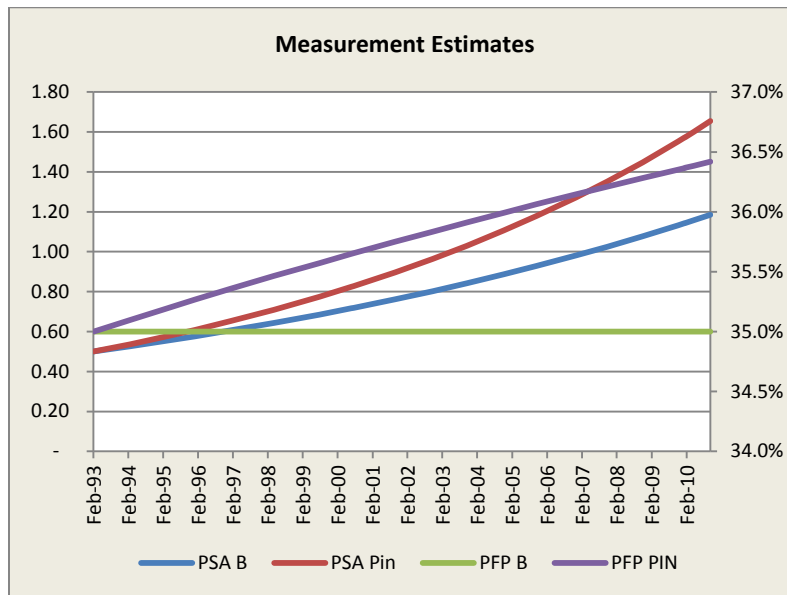
The next issue is to establish a baseline for the incidence of any of these states, namely when do we measure X0. For simplicity we assume at 50 that all X0 are the same, based on a 40 year old baseline. This is one of the concerns with this model, namely

establishing a baseline. We argue that similar estimation techniques can provide that as well.

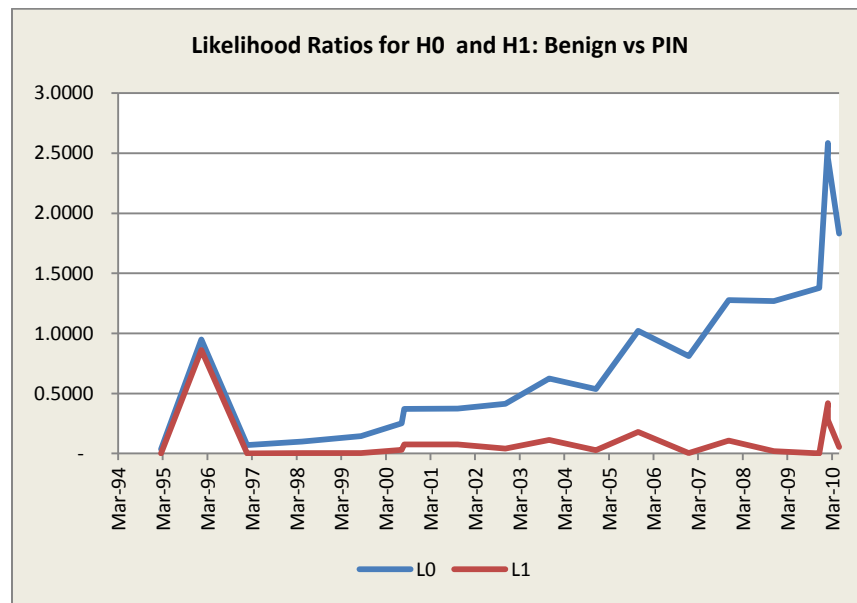
We now use this on the data we have shown earlier. First we show the call growth under two assumptions:



Then we show the projected measurement values to be used against the real measurements.



Then we show the likelihood ratios. Remember the selection is the smallest value based on it yielding the largest likelihood.



The interesting metric is the fact that we have a growing likelihood that the data suggests even five years earlier that PIN was present.

Thus we have shown that this maximum likelihood approach as modified appears to be readily applied and provides a strong suggestive set of guidelines for the physician.

## 6 CONCLUSIONS

We have developed an alternative approach to the use of the limited data for assessing the risk of PCa in patients. It is an approach which is based upon the underlying dynamics of the cellular system and reflects the impact of key parameters of different cell growth rate and their impact on the measured variables. We have also shown that

1. The new metric requires a long period of collecting data on PSA and PFP. It then requires having reliable data on growth in the four differing scenarios. However it is interesting in that by including the data in this form we are effectively including velocity data implicitly.
2. The underlying constants may be based upon other factors as well, namely race, family history, and age. The Punglia paper does look somewhat at age segregation and recommends lower thresholds. We argue here that a running statistic may provide an improved discriminant.
3. ROC characteristics can be calculated analytically from this approach assuming certain constants.

4. The approach is direct and simple and seems to allow for early detection via a tracking of the likelihood ratio.

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