The Prostate Specific-Antigen (PSA):

Why it could not detect prostate cancer reliably in the past

and

How it became a sensitive and specific tumor marker

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0. Summary

PSA consists generally of two long term components PSA_{BPH} (due to Benign Prostate Hyperplasia) and PSA_{PCa} (due to Prostate Cancer). The two components cannot be distinguished either chemically or physically. Dedifferentiated cells, however, divide at constant time intervals and the doubling times of PSA_{BPH} and PSA_{PCa} differ considerably. Thus a mathematical rule permits an individual evaluation of the two components.

Software developed by the author applies this mathematical procedure to split up measured PSA levels into their two components providing reproducible proposals for diagnosis/prognosis concerning BPH and/or PCa. These proposals appear in a completely new form of presentation i.e. graphs easily understood by everyone just at a glance.

1. Facts known for 21 years

In 1987 and 1989 T. A. Stamey et al. published the papers [1] and [2] and in 1993 a review [3] by H.-P. Schmid et al. appeared.

The first two papers make it clear that BPH as well as PCa contribute to the PSA level, although it is not possible to measure these components directly. – The third paper adds valuable information as to what minimum volume of PCa could be detected with the aid of PSA.

NOTE: The lack of knowledge concerning individual values of the components precludes a reliable diagnosis “PCa” and/or “BPH”. Knowing only the total PSA level is the reason for all problems with PSA in the past: It cannot even tell us, whether one or two components are involved or give us a reason to think “it looks suspiciously like PCa”!

Splitting up the PSA level into its two components PSA_{BPH} and PSA_{PCa} is a must: A method including software to achieve this has been developed by the author so that the ‘unknown mix of PSA_{BPH} and PSA_{PCa} needs and should no longer be used!

2. How to separate PSA_{BPH} and PSA_{PCa}

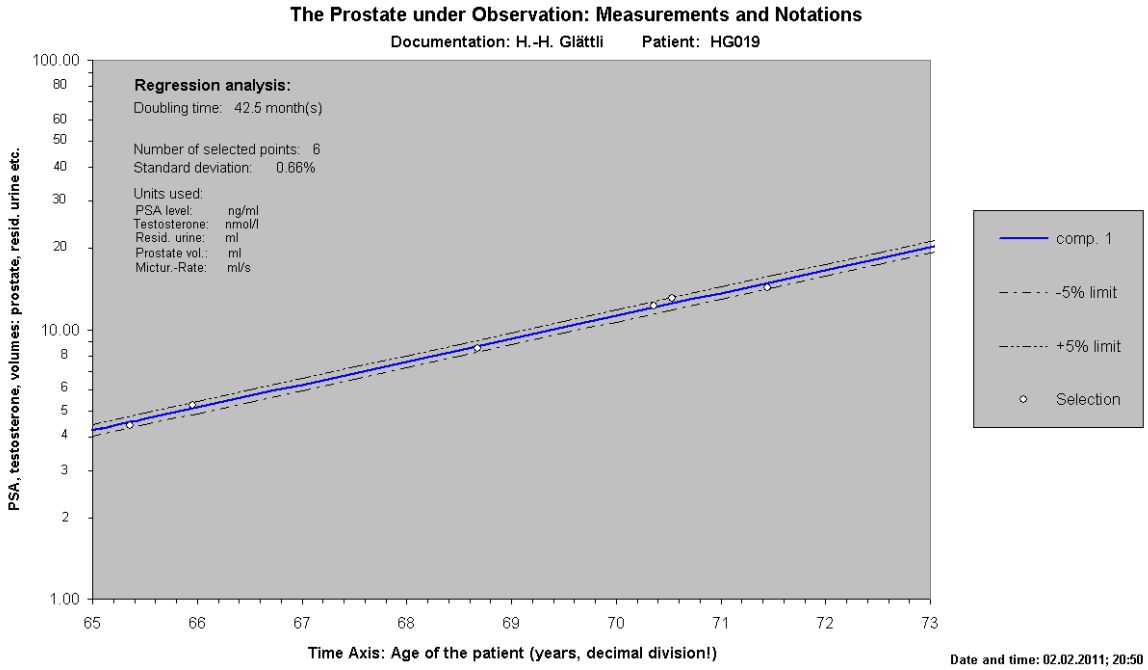
Remembering that undifferentiated or dedifferentiated cells divide at constant intervals was a great help in finding the solution: If BPH and PCa behave like this both follow an exponential dependence on time and the sum of both influences, however, does no longer represent an exponential function.

Mathematics (see [4] and [5]), however, tells us that a sum of two exponential functions can easily be split up into their components. What we have to do prior to applying the necessary routine is to prove that BPH and PCa behave exponentially with time.

Measured PSA levels to be processed have to be selected on an individual base (see symbol), unselected PSA-levels would appear as black rhombs. The same units have been used throughout.

3. BPH and PCa follow an exponential dependence on time!

This statement can be proven easily by examining the following type of diagrams: In semilogarithmic graphs an exponential function is represented by a straight line as shown in Fig. 1 illustrating the behaviour of BPH:

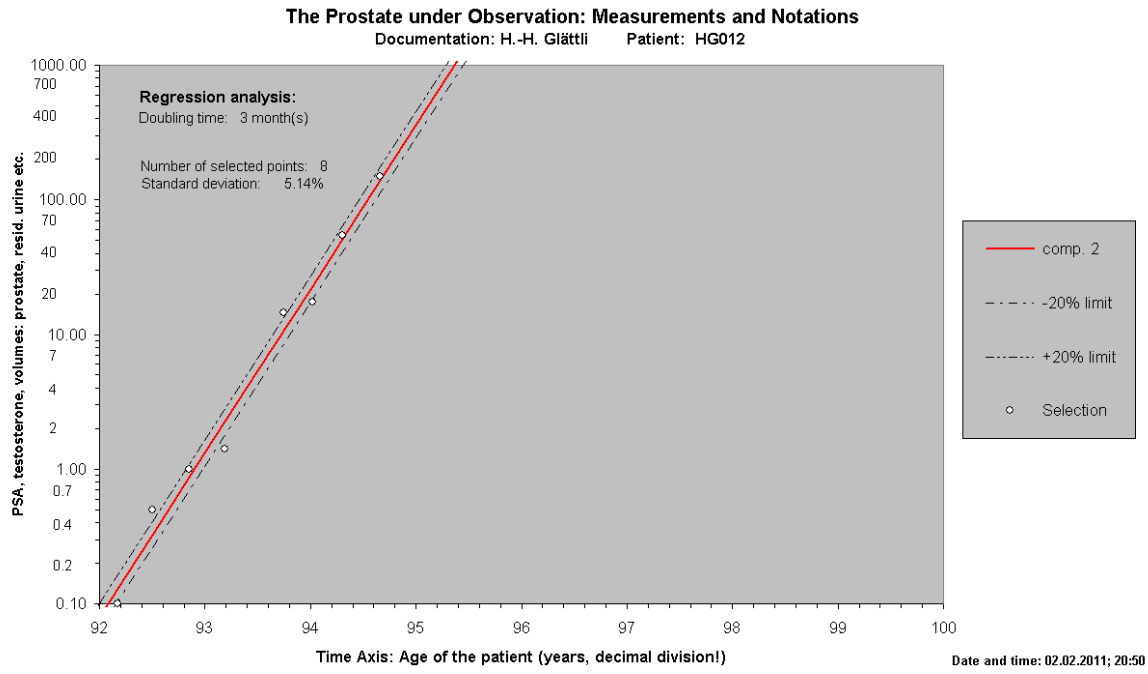


BPH follows an exponential dependence on time

Fig. 1

It shows just one of any number of examples: Over a period of more than six years the PSA level stays within ±5% with respect to a straight line determined by regression analysis. The most frequent doubling time for BPH lies between six and eight years. Every graph uses the same legend, although some variables are not shown! See annex!

Fig. 2 shows another example referring to a recurrent PCa:



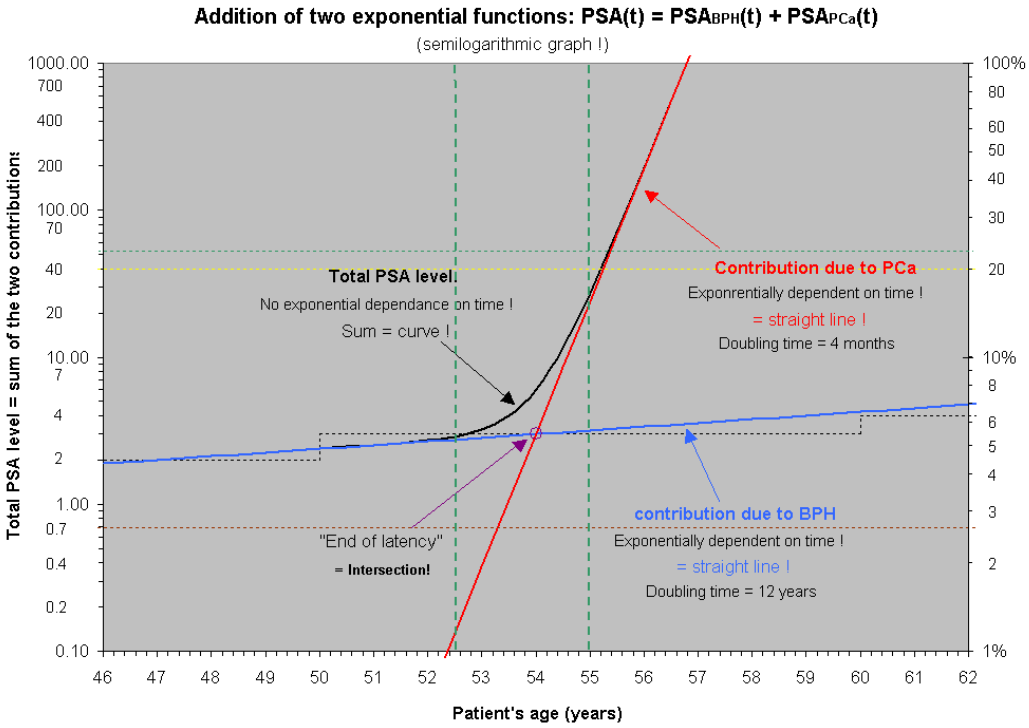
PCa follows analogously an exponential dependence on time

Fig. 2

Analogously to Fig.1 PCa (in this case after radical prostatectomy) also causes the PSA level to follow an exponential dependence on time: The doubling time of three months, however, is much shorter than in the case of BPH. – This observation reflects a very important difference between BPH and PCa as will be made use of later.

4. The procedure to distinguish between PSA_{BPH} and PSA_{PCa}

The next step is to find out what curves may look like in graphs representing a superposition of two exponential functions as shown in the first two figures: It was found that their shape as shown in Fig.3 is very characteristic and cannot be confounded with any other phenomenon:



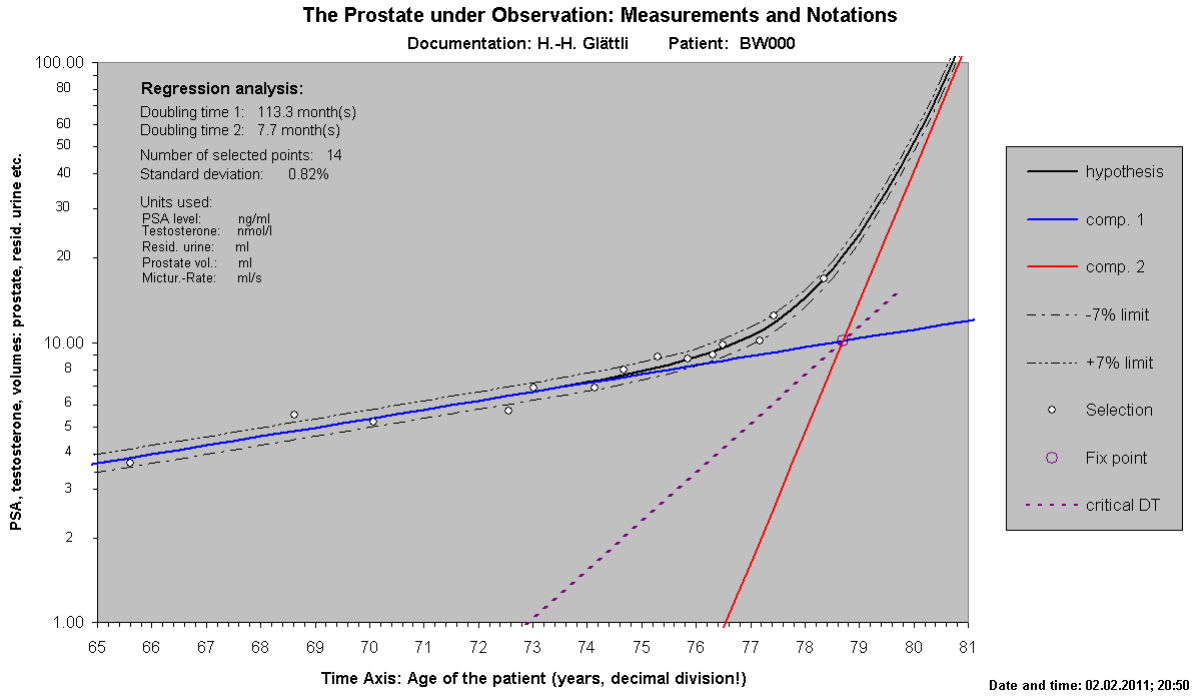
Superposition of two exponential functions due to BPH and PCa
Fig. 3

The shape of such a curve constructed mathematically may be described as follows: If we start measurements early enough the curve representing the PSA level as a function of time begins as a straight line rising slowly. As soon as PCa becomes detectable the curve tends to become gradually steeper and finally continues as another straight line characterized by a higher slope similar to the one seen in Fig. 2.

Looking at any number of observations this typical shape is confirmed qualitatively without exceptions: The slope of the two parts following a straight line may differ quantitatively and the radius of the curvature will be shorter when the second exponential function rises faster (=more aggressive PCa!). The dashed black line shows the age-dependent critical PSA levels proposed earlier by Oesterling (now meaningless!).

The portion between the two green dashed lines is of special interest: Only In this part of the graph the black curve is influenced by both components allowing us to look back into the past, as well as to look into the future. At the left of this middle section there is no chance to recognize signs of PCa and at the very right the past can no longer be reconstructed.

Fig. 4 shows a practical example:



Early recognition of PCa: PSA levels split up into the components PSA_{BPH} and PSA_{PCa}
Fig. 4

Software developed by the author has been applied to the measured PSA levels. It splits up the experimental curve into its two exponential functions PSA_{BPH} and PSA_{PCa} and applies regression analysis to produce a smooth black curve showing the measured PSA levels. At the same time the doubling times of the two components PSA_{BPH} and PSA_{PCa} are determined and numerically introduced into the diagram.

The software compared the slope of the first component with the one of the violet dashed line and recognized that doubling time 1 is too long for PCa and drew the corresponding straight line (=first exponential function) in blue; doubling time 2 of the second exponential function was found to be too short for BPH; therefore the line is drawn in red. The critical doubling time is represented by the slope of the dashed violet line (calculated on the basis of the patient's age and the volume of his prostate). It's purpose therefore is to discriminate between BPH and PCa.

As a result the software works out automatically a proposal for a diagnosis/prognosis as follows: "BPH" (doubling time = 113.3 months) and "PCa" (doubling time = approximately 7.7 months) becoming detectable at the age of some 77 years due to its deviation from the blue line. Verification must follow with the aid of a biopsy or DNA cytometry.

Automatically produced results are possible due to the following facts:

1.	Both BPH and PCa depend exponentially on time. Consequently (and according to mathematical rule) we can split up a sequence of measured PSA levels into the two components PSA_{BPH} and PSA_{PCa} (a minimum of four measurements are required).
2.	The marked difference of the doubling times permits identification of PSA_{BPH} and PSA_{PCa}.

The doubling times involved change very slowly and therefore allow to extrapolate the curve as well as the straight lines into the future providing a good prognosis for doctors and patients. The database combined with the software was designed to have a capacity of 10 000 medical histories.

5. Conclusions based on more than 1375 medical histories

During seven years the author obtained more than 1375 medical histories; all of them served for careful tests; no principal failure could be detected. Some precautions, however, have been derived to improve the efficacy of determining the PSA levels: Measurements should best occur at regular time intervals (clusters make no sense).

A.	The two phenomena BPH and PCa can be observed independently, quantitatively and unambiguously as a function of time,
B.	The additional information with regard to biopsies allows us to recognize PCa in need of treatment,
C.	A combined diagnosis/prognosis is presented in a completely new form of software generated graphs easily understood within seconds by doctors as well as by most of the patients.

Furthermore it is easily possible to recognize at least the following phenomena:

a.	Prostatitis (characteristically falling PSA levels during therapy with antibiotics!),
b.	Partially or totally unsuccessful therapies (the behaviour of PSA is not influenced or PSA level rise characteristically after the PSA secretion was “cured” instead of the carcinoma,
c.	Tumor progression (the PSA curve turns upwards from the straight orange line representing an exponential function and becomes steeper illustrating a gradual shortening of the (final) doubling time which approaches a new constant value).

6. References

[1]	Stamey TA, MacNeal JE, Freiha FS, Redwine E.: Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987; 317, October, 909-16
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[3]	Schmid HP, McNeal JE, Stamey TA. Observations on the Doubling Time of Prostate Cancer. CANCER, Vol. 71, No. 6, March 15, 1993
[4]	Gerber Hans-Jürg: http://precedings.nature.com/documents/3930/version/1 2008
[5]	Hans-Heinrich Glättli, Juergen Durner, Hans-Jürg Gerber: Is it Prostate Cancer? http://hdl.handle.net/10101/npre.2010.4556.1 2010
[6]	Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA. 1993; 270: 860-4

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