Brief Communication

PSA Dynamics traditionally evaluated with an inadequate formula

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Abstract.
The PSA doubling time is usually calculated from measured PSA values with an inadequate formula that tacitly assumes the absence of that process, which it is supposed to reveal. We present a modified calculational procedure which is optimized to unveil a weak second exponential process in the presence of a strong first one, using early screening data. The notion of Break Even Time (BET) indicates the stages of the processes.

We assume that four or more measured Prostate-Specific Antigen (PSA) levels have been caused by two simultaneous independent exponential processes with different characteristic doubling times, DT1 and DT2, the latter being of our main interest. We do not assume any previous knowledge of the stages of these processes, the expected results for the DTs shall be independent of them.
The time-dependent PSA concentration is then of the form $PSA(t) = a\, e^{\alpha t} + b\, e^{\beta t}$, with the relations $DT1 = \ln(2)/\alpha$ and $DT2 = \ln(2)/\beta$. The constants α and β are thus characteristic for the producing cells, whereas a and b depend on the number of acting cells and on various, mostly unknown, efficiencies. If the first process alone would be in action (b=0), then the PSA(t) curve would, on a logarithmic scale, be a straigth line with a slope characteristic for DT1 . From two points at t and t_0 we derive the "common formula"
$DT(t) = (t - t_0)\, \log(2)/(\log(PSA(t)) - \log(PSA(t_0)))$.

If this formula is uncautiously used in the case, where two competing processes are present, the value obtained for DT(t) becomes misleading, since it has no more an interpretable significance with repect to the result of our interest.Due to the mathematical property that $DT(t) \rightarrow DT2$ for $t \rightarrow \infty$ (when $\beta > \alpha$), the result of DT(t) correctly approaches DT2, but at a later time, possibly whem it is no more urgently needed. It is especially unspecefic at the interesting moment when the second process starts to become visible.We may even suspect, that this deficiency, which causes enhanced artifacts in the PSADT results, contributes to the controversial interpretations concerning the benefit of PSADT knowledge at all.
Our approach is, to search for the curve PSA(t) which is best adapted to the measured PSA data, and we extract at once the four values of a, α, b, β, which in turn are used for practical conclusions. See the *Fig. 1*.
We expect, that the value of β has a high specifity for the second process, by design, and that it is fairly independent, as well of the properties of the first process as of their stages, by the conduct of the formal procedure.
For an indicator of of the stages of the processes, we may define the time, when the second process has grown so strong as to contribute the same amount of PSA, as does the first one, i.e. half of the total. Calling this time "BET" = Break Even Time, we find
$BET = 2.30 \times \log10(a/b) / (\beta - \alpha)$. This formula makes use of information on the relative developpment stage of the cell ensembles. Since the ratio (a/b) enters, we expect that common unknown factors in the two processes cancel and the result thus becomes more stable. We may think of partly using the first process as a calibration for the second one. This emphasizes the necessity of the early measurements (in our case, at t = 0 and 54 months).
The sensitivity and the reliability of the result for DT2 is studied by answering the question: "Could the second process have been discovered earlier, based on the data after 3, 4 or 5 PSA measurements already ?"

The points representing the values of the 3 earliest PSA measurements are found to well lay on a straight line, considering an uncertainty of $\pm$ 4 % (std, normal) indicated by the size of the circles in *Fig. 1*. This is characteristic for one single exponential process.
The 4th point (at t = 105 months) clearly deviates from a straight line and thus hints at a second process. The result of our analysis yields the parameters of this process, and predicts the time (BET), when it will have reached an equal PSA-production power to the first one. The 5th and 6th measurement confirm the the results for DT2 and BET. A criterion for the applicability of the function PSADT(t) and thus of the method proposed here, is provided automatically in each single case by the goodness-of-fit result of the least squares analysis.

As a comparison we also give the values calculated with the common formula. See. *Fig. 2*. With an official PSADT calculater published in the internet, a misleading result which exceeds our DT2 by a factor of 5 has been found.

In order to obtain a useful tool from our procedure, DT2 and BET have to be calibrated versus diagnostic findings. Due to the formal stability of these notions and their direct significance in terms of the more general model with two exponentials, we may expect more strict correlations than the ones obtained with the presently used dynamic parameters.

FIGURE CAPTIONS

Fig.1. Evidence for two exponential processes. Break Even Time BET determined.
The curve is a weighted least squares fit of the function PSA(t) to a real patient's PSA data points. It is the sum of the two straigth lines that reveal the two exponential processes. They are widely different in their original strengths and their slopes. At time *t* = BET, the processes are of equal strenth.Their Doubling Times DT1 = 66 months, DT2 = 7 months, and BET = 117 months arise in turn as a result from the least squares procedure. The "common formula" applied to the latest two points would yield the irrelevant value of DT(116) = 18.5 months.

Fig. 2. How well is the Doubling Time DT2 predicted after 4, 5 or 6 PSA measurements ?
Already with the 4^{th} measurement at t = 105 months, a second process is identified. Its doubling time DT2 is estimated to be 7.5 ± 6.4 months (std) with a BET of t = 120 months. The later measurements confirm this finding with improved accuracy. The "common formula" yields the values labelled "Common F". They do not show convergence towards an interpretable value (yet).

FIGURE 1 of the paper “PSA Dynamics traditionally evaluated with an inadequate formula”

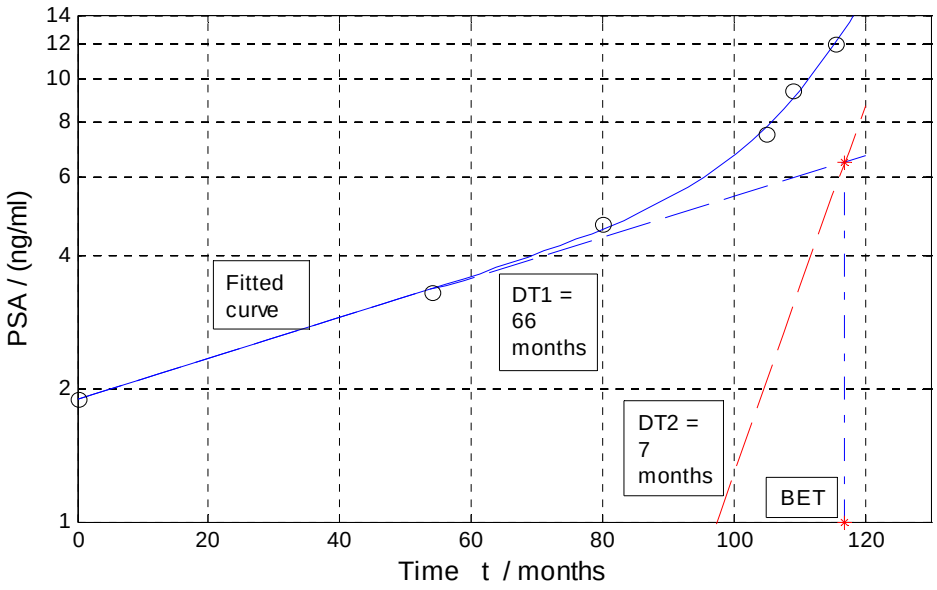

FIGURE 2 of the paper “PSA Dynamics traditionally evaluated with an inadequate formula”