# Supplementary Document 1 - General Expression for the Variance of the Single Reference-Variable Flip Angle Dynamic T1 Calculation

# Overview

The following is the general expression for the variance equation of the single reference (SR) variable flip angle (VFA) method’s dynamic T1 calculation, both with and without a correction for dynamic T2\* changes. The initial SR-VFA method was presented by Svedin *et al*. in 20191.

First, we begin with the statement of the variance based on the theory of propagation of errors, and similar to the analysis presented on the standard two-flip angle version of the variable flip angle (VFA) method2. The independent variables upon which the calculation depends are the signals, giving the following for the variance of the T1d estimate:

|  |  |
| --- | --- |
|  | (Eq. S1-1) |
|  | (Eq. S1-2) |

where refers to the signals of type *i* (i.e., images acquired at different flip angles and/or dynamic times) at echo time *j* , k is the echo time of the T1d map of interest, x is the relative fraction of that signal type/echo combination relative to the total number of signals, N, and . For this work, Ntypes = 3, where types 1 and 2 refer to signals acquired at T1,baseline at two different flip angles, and type 3 refers to signals acquired at T1d at the same flip angle as type 2 signals.

For clarity, T1d will hereafter denote the true dynamic T1 value. The calculated dynamic T1, T1d,est, will be distinguished from this true value in the derivation. However, in the absence of noise in the measured signals, the value of T1d,est for the T2\* corrected SR-VFA method (SR-VFA-T2\*) is theoretically equivalent to T1d. E1 will hereafter refer to E1 at baseline, meaning E1d is the dynamic versions of E1, . E2 and E2d are defined similarly , but also include the subscript k to refer to their value at a specific TEk: ,

## Calculation of a Dynamic T1 estimate (T1d,est­) with the SR-VFA method

The equation for T1d,est is as follows:

|  |  |
| --- | --- |
|  | (Eq. S2-1) |

Where each dynamic T1 map acquired at echo time k, *T1d,est,k*, is combined with inverse variance weighting to produce one dynamic T1 map from multi-echo data. The weighting for each echo time, *wk,* is given as follows:

|  |  |
| --- | --- |
|  | (Eq. S2-2) |

Combining Equation S1 with S2-1 and S2-2 yields:

|  |  |
| --- | --- |
|  | (Eq. S3) |

The calculation of a dynamic T1 map at a single echo time can then be written as follows:

|  |  |
| --- | --- |
|  | (Eq. S4-1) |
|  | (Eq. S4-2) |
|  | (Eq. S4-3) |
|  | (Eq. S4-4) |
|  | (Eq. S4-5) |
|  | (Eq. S4-6) |

Note that is an estimate of the true value of . When this estimate is set to 1 and when only one echo time is used, this expression becomes equivalent to that originally presented by Svedin *et al.*1.

# Part 1-1 – Overview

In this expression, has already been defined by Equations S4.1 to S4.6, and *wk ­*was defined in Eq. S2-2. Thus the only undefined terms are the two derivatives, and . We begin with .

|  |  |
| --- | --- |
|  | (Eq. S5) |

Given the definition of 𝜔 above and cancelling the negative sign, as well as acknowledging that ln(𝜔) = -TR/T1d,est, k, we get the following:

Which simplifies to Equation S6:

|  |  |
| --- | --- |
|  | (Eq. S6) |

I now define a new combination variable as follows:

|  |  |
| --- | --- |
|  | (Eq. S7) |

Making the T1d,est variance equation thus far:

|  |  |
| --- | --- |
|  | (Eq. S8) |

## Expansion of λ((E2d/E2)est,k)

With this in place, I can write the two specific cases of interest for the expression λ(E2d/E2)est,k .

Special Case 1: ((E2d/E2)est,k = 1)

|  |  |
| --- | --- |
|  | (Eq. S9) |

Special Case 2: ((E2d/E2)est,k = (E2d/E2)k):

|  |  |
| --- | --- |
|  | (Eq. S10) |

# Part 1-2 – ∂γk/∂Si,j

With these defined, we move on to define the derivatives and from Equation S8. Notice that and are both calculated parameters from the signal values. Beginning with ,

|  |  |
| --- | --- |
|  | (Eq. S11) |

## Further expansion of derivatives for dγk/dSi,j

The derivatives inside Eq. S11 can be further simplified:

|  |  |
| --- | --- |
|  | (Eq. S12) |

And

|  |  |
| --- | --- |
|  | (Eq. S13) |

### Expansion of ∂/∂Si,j{E1} and ∂/∂Si,j{E1est,k}

To further simplify the derivatives in Equations S12 and S13, we first note Equations S4-4 to S4-6 that define the calculated E1 and E1,est as functions on a ratio of two signals

|  |  |
| --- | --- |
|  | (Eq. S14) |

Also,

|  |  |
| --- | --- |
|  | (Eq. S15) |

and

|  |  |
| --- | --- |
|  | (Eq. S16) |

Now to define and .

|  |  |
| --- | --- |
|  | (Eq. S17) |

If the spoiled gradient echo equation is inserted into Equation S17, the following simplification results:

|  |  |
| --- | --- |
|  | (Eq. S18) |

From similar analysis,

|  |  |
| --- | --- |
|  | (Eq. S19) |

This can be expanded using the spoiled gradient echo equation to get the following:

And recalling Equation S16, the denominator can be written as , giving us

|  |  |
| --- | --- |
|  | (Eq. S20) |

## ∂γk/∂Si,j in Simplified Form

From these, we can rewrite Equation S11 as Equation S21:

|  |  |
| --- | --- |
|  | (Eq. S21-1) |
|  | (Eq. S21-2) |

### ∂γk/∂Si,j further expansion (optional subsection)

At this point, if the exact values of the parameters are not known, such as in real scans, then the noisy signal values with the flip angles can give you an approximate measure of this value . This is employed in the final result for obtaining weights for quasi-optimal T1-map combination at each echo time. However, if the true values are known, then they can be substituted in as shown below with the continued derivation.

Now for the other two signal types, things are a little easier:

Since the second term’s dependence on is 0, only the first term remains:

Now for

The first term’s dependence on S3 is 0, so only the second term remains. Recall the formula for .

## Variance Equation for negligible T2\* change (*i.e.* SR-VFA method, E2d/E2 = 1)

If no T2\* change is assumed, then , and we use *λ*(1) and a single echo time, we can finish the expression for the SR-VFA T1d,est variance by combining Equations S1, S8, S9 and S21.

|  |  |
| --- | --- |
|  | (Eq. S22) |

In this form, the variance can be obtained directly from the signal measurements themselves and their derivatives (E1 and E1est). When this is further expanded with the spoiled gradient echo equation, it becomes the following:

# Part 1-3 -

## Definition of (E2d/E2)est,k

Now I can move on to . This is needed for the SR-VFA-T2\* method that corrects for the T2\* changes during the dynamic acquisitions. can be defined as follows:

|  |  |
| --- | --- |
|  | (Eq. S23) |

results from the linear least squares fit of the signal values of type 1 averaged with the linear least squares fit of the signal values of type 2

=results from the linear least squares fit of the signal values of type 3

Since this T2\* correction is applied to each echo’s calculated T1 value, I need to distinguish between echo times of the different signals. For the T2\* correction on the T1 value, in which multiple estimates of T1 from different echo times’ calculations are first corrected and then linearly combined to achieve greater precision, E2d/E2 then changes for each echo time k, since E2 = exp(-TE/T2\*) and E2d = exp(-TE/T2d\*)

So

|  |  |
| --- | --- |
|  | (Eq. S24) |

## Expressions for T2\*est and T2d\*est

Now we move on to the definitions of and .

Assuming a linear least-squares fit of multi-echo data to determine the exponential parameter T2\*, I can consider the least squares solution for T2\* from a simplified model of the original spoiled gradient echo equation:

|  |  |
| --- | --- |
|  | (Eq. S25-1) |

Given this simplified signal equation, I can write another linearized form:

|  |  |
| --- | --- |
|  | (Eq. S25-2) |

Or in matrix notation:

|  |  |
| --- | --- |
|  | (Eq. S25-3) |

In this form, I can solve for the least squares best fit of the matrix x by performing the matrix operations in Eq. S26:

|  |  |
| --- | --- |
|  | (Eq. S26) |

Doing this results in the following:

|  |  |
| --- | --- |
|  | (Eq. S27) |

However, since we are only interested in the term that leads to T2\*, we can focus solely on the top term of the x matrix, since x(1) = -1/T2\*. Thus:

And rewriting with the previous signal notation to account for only types 1 and 2 in this baseline T2\* measurement:

|  |  |
| --- | --- |
|  | (Eq. S28) |

Assuming every echo time from both baseline signal types is used to calculate the baseline estimate of T2\*, then I can rewrite the definition of to be dependent on all echoes of both signal types 1 and 2. For simplicity, the T2\* estimates from signal types 1 and 2 will be averaged together. Thus:

|  |  |
| --- | --- |
|  | (Eq. S29) |

It follows directly that the definition of is equivalent to the Equation S28 , with the signals included being those echoes of the dynamic measurement (type 3).

|  |  |
| --- | --- |
|  | (Eq. S30) |

## Derivatives of T2\*est and T2d\*est

Now that I have an expression for T2\*est and T2d\*est, I can determine the derivative of each with relation to each signal.

Notice that from this expression, as expected, the first term drops out when i ≠ 1, and the second term drops out when i ≠ 2. Additionally, the derivative will only be nonzero if j = m .Thus, the above derivative can be simplified as follows with two non-zero cases:

|  |  |
| --- | --- |
|  | (Eq. S31-1) |
|  | (Eq. S31-2) |

The derivative of proceeds in a similar fashion:

Similar to the above, the derivative is only non-zero when i = 3, and thus the equation simplifies as follows:

|  |  |
| --- | --- |
|  | (Eq. S32-1) |
|  | (Eq. S32-2) |

## in Simplified Form

Now we can write the full expression for by utilizing Equations S24, S31, and S32. First we define another variable for more concise notation:

|  |  |
| --- | --- |
|  | (Eq. S33) |

Then the full expression for is written as Equations S34-1 through S34-3

|  |  |
| --- | --- |
|  | (Eq. S34-1) |
|  | (Eq. S34-2) |
|  | (Eq. S34-3) |

# Part 1-4 Final Expression for

We finish the expression for by listing Equations S1-2 and S8 with the equation numbers of all the other relevant definitions:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |
| *Relevant Equations* | S4-1  S4-2  S4-3  S4-4  S4-5  S4-6  **S7**  S23 | **S23**  S28  S29  S30 | S4-4  S4-5  S4-6  **S21** | **S4-3**  S4-4  S4-5  S4-6 | S33  **S34-1**  **S34-2**  **S34-3** |
| Note: A **Bolded** equation number indicates the direct definition of the variable. | | | | | |

# Part 2-1 – ∂wk/∂Si,j Overview

To find the variance of the linear combination described in Equation S3, one other derivative, , needs to be expanded. First, we rewrite the expression for the inverse variance weighting factor found in Equation S2-2:

Taking the derivative with respect to the signal yields the following:

Simplifying and reordering the sum to be outside the derivative,

This further simplifies to Equation S35:

|  |  |
| --- | --- |
|  | (Eq. S35) |

From here, the variance terms not inside a derivative are given in Part 1 of this document. The only remaining derivative to simplify is the bolded

# Part 2-2 – More Derivatives

From Part 1, we have the equation for the variance with respect to each signal:

Taking the derivative yields the following. Subscripts were changed in the above variance expression because the desired derivative needs to be the variance (which is a conglomerate of signal effects) with respect to every signal.

|  |  |
| --- | --- |
|  | (Eq. S36) |

From here, only the last bolded derivative needs to be expanded, since is already known with just a change of subscript notation.

|  |  |
| --- | --- |
|  | (Eq. S37) |

Now, there are three more bolded derivatives to be expanded. We start with

## Expansion of

Remembering the definition of λ from Equation S7:

|  |  |
| --- | --- |
|  | (Eq. S38) |

## Expansion of

Now we can move on to . First, we remember the definition of from Equation S21-2.

To take this derivative, E1 and E1,est,k must be recognized as calculated quantities, and the constants can be removed as follows:

Simplifying this expression requires simplifying several intermediate derivatives, shown below with simplifications done by using Equations S18 and S20.

These allow us to expand and simplify the earlier expression. We define some new variables to make this equation less cumbersome:

|  |  |
| --- | --- |
|  | (Eq. S39) |

## Expansion of

Now we can move on to the final of the three needed derivatives, . Remembering Equations S24 for the definition of , we write the following:

|  |  |
| --- | --- |
|  | (Eq. S40) |

Now there remain only two derivatives to be expanded: and

### Expansion of and

We now use Equations S31 and S32 as a starting point for the derivatives and .

Recalling the definition of from Equation S28

It is clear that this derivative is only nonzero when i=p. Thus:

|  |  |
| --- | --- |
|  | (Eq. S41-1) |
|  | (Eq. S41-2) |

Again note that in the right-hand side of Equations S41-1 and S41-2, is used instead of . Their relationship was given previously in Equation S29. Using Equation S30 and following a similar analysis for the case i=p=3:

|  |  |
| --- | --- |
|  | (Eq. S42-1) |
|  | (Eq. S42-2) |

# Part 2-3 – Final Expression for

For the final variance expression, we list Equations S3, S35, S36, and S37 while listing their relevant equations:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | Other necessary variables |
| *Relevant Equations* | **S4-1**  S4-2  S4-3  S4-4  S4-5  S4-6 | S2-1  **S2-2** | S4-1  S4-2  S4-3  S4-4  S4-5  S4-6  **S38**  Part 1-4 | S4-4  S4-5  S4-6  **S39** | S28  S29  S30  S31-1  S31-2  S32-1  S32-2  **S40** | see Part 1-4 of this document | |
| Note: A **Bolded** equation number indicates the direct definition of the variable. | | | | | | | |

## References

1Svedin, B. T., Payne, A., & Parker, D. L. (2019). Simultaneous proton resonance frequency shift thermometry and T1 measurements using a single reference variable flip angle T1 method. *Magnetic Resonance in Medicine*, *81*(5), 3138–3152. <https://doi.org/10.1002/mrm.27643>

3Schabel, M. C., & Morrell, G. R. (2008). Uncertainty inT1mapping using the variable flip angle method with two flip angles. *Physics in Medicine and Biology*, *54*(1), N1–N8. <https://doi.org/10.1088/0031-9155/54/1/N01>