2.4 Theoretical Background

To approach the widely used Modified-Beer Lambert Law (MBLL), the unmodified Beer-Lambert Law (BLL) will be briefly introduced and then expanded.
The original BLL describes a simplified case in which light is sent through a volume filled with only one absorbing compound dissolved in a non-absorbing solvent, as is the case in an in vitro spectrophotometric analysis.

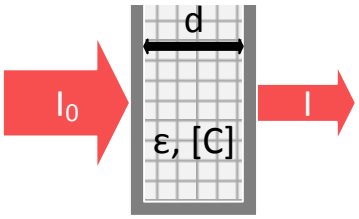

Figure 2.7: Cuvette model for Beer-Lambert Law for in vitro spectrophotometric analysis.

For such a *cuvette model* (see fig. 2.7), the BLL states that the attenuation A of an interrogating monochromatic energy with incident intensity I_0 is proportional to the product of the compound's concentration c in mol, its molar extinction coefficient ϵ_λ, and the optical path length d

$$I = I_0 \cdot 10^{-\epsilon_\lambda cd} \Leftrightarrow A = -\log_{10}\left(\frac{I}{I_0}\right) = \epsilon_\lambda cd. \tag{2.1}$$

In practice, samples have usually more absorbers than one. To determine the concentration of each of the i chromophores, measuring at i wavelengths and setting up a system of equations is necessary. Furthermore, chromophore concentrations are time-dependent and as in case of fNIRS optodes, the optical path length is not straight and equal to the distance d between light emitter and receiver but often assumed to be banana-shaped (see [12] for further investigation of the light path) and has to be corrected by the *Differential Pathlength Factor - DPF*:

$$A(t,\lambda) = -\log_{10}\left(\frac{I(t,\lambda)}{I_0(t,\lambda)}\right) = \sum_{i=1}^{n} \epsilon_{i\lambda} c_i(t) DPF(\lambda) d \tag{2.2}$$

Since this law does not take scattering into account, it is still solely applicable to interrogated volumes in which only absorption takes place, and can thereby not be used for tissue interrogation. To improve this, Delpy et al. modified the BLL by adding a *scattering dependent light intensity loss parameter* G [2].

$$A(t,\lambda) = -\log_{10}\left(\frac{I(t,\lambda)}{I_0(t,\lambda)}\right) = \sum_{i=1}^{n} \epsilon_{i\lambda} c_i(t) DPF(\lambda) d + G(\lambda) \tag{2.3}$$

With G in the equation, chromophore concentrations cannot be calculated without knowing the scattering influence. Instead, Delpy et al. proposed to calculate the chromophore concentration changes by building the difference of two measurements from an initial time

point t_0 and a consecutive timepoint t_1 using the modified Beer-Lambert Law, thereby removing the scattering influence G from the equation and also canceling out the emitted intensity I_0, which is constant:

$$\Delta A(\Delta t, \lambda) = -\log_{10}\left(\frac{I(t_1, \lambda)}{I(t_0, \lambda)}\right) = \sum_{i=1}^{n} \epsilon_{i\lambda} \Delta c_i(t) DPF(\lambda) d \tag{2.4}$$

When oxy-hemoglobin and deoxy-hemoglobin are evaluated at two wavelengths and two consecutive points in time, the resulting system of equations can easily be solved for the changes in concentrations Δc_i. The concentration changes of HbO and HbR are then given by

$$\begin{bmatrix} \Delta[HbR] \\ \Delta[HbO] \end{bmatrix} = \frac{1}{d} \cdot \begin{bmatrix} \epsilon_{HbR,\lambda_1} & \epsilon_{HbO,\lambda_1} \\ \epsilon_{HbR,\lambda_2} & \epsilon_{HbO,\lambda_2} \end{bmatrix}^{-1} \begin{bmatrix} \frac{\Delta A(\Delta t,\lambda_1)}{DPF(\lambda_1)} \\ \frac{\Delta A(\Delta t,\lambda_2)}{DPF(\lambda_2)} \end{bmatrix} \tag{2.5}$$

Using the MBLL for the determination of relative chromophore concentrations in the brain, several assumptions have been made which were identified and discussed by Obrig and Vilbringer [35] and Boas [45].

1. **The change in scattering is small compared to the change in absorption**: This permits to disregard G in the step of equation 2.4 and allows to assume the DPF at certain wavelengths to be constant. This assumption is generally assessed plausible.
2. **The medium in which changes are monitored is homogeneous:** Being clearly a wrong assumption, this is seen to be one reason for the low spatial resolution of non-invasive NIRS compared with invasive optical techniques.
3. **The change of parameters of interest (especially chromophore concentration) is homogeneous within the sampling volume:** Related to the assumption above, this is also wrong: Besides the cortical region, the sampling volume consists of scalp and skull. Therefore, the region of hemoglobin change is relative to the entire sampling region. This introduces an additional source of error stemming from the wavelength dependence of the DPF in the signal.

Despite the MBLL being only a reasonable first approximation, almost all CW approaches so far are based on it [35]. This is predominantly justified by the focus of interest in brain research being much more on the trend of the signals than on its quantification [11]. So far, its "validity [...] has tested favorably against several other monitoring modalities and theoretical studies suggest that any resulting errors can be limited to less than 10%" [13].

To use the MBLL, several parameters have to be specified and were subject to theoretical and experimental research predominantly in the 90s. The extinction coefficients of the chromophores were determined in vitro using laboratory spectrophotometers and can be looked up in tables such as in [21]. For CW technology, which does not enable the direct measurement of optical path lengths such as in FD and TD systems, particularly the DPF was both experimentally and numerically investigated. Findings were that the DPF is age, gender- and wavelength-dependent, varying up to 15% between subjects with a mean value of 6.53 ± 0.99 [46, 47].

Okada et al. compared experimental measurements on phantoms with mathematical predictions by Monte Carlo Method and Finite Elements Method on four models [31] to

determine sensitivity profiles dependent on the partial optical path lengths in the different types of tissue and source-detector spacing (see fig. 2.8).

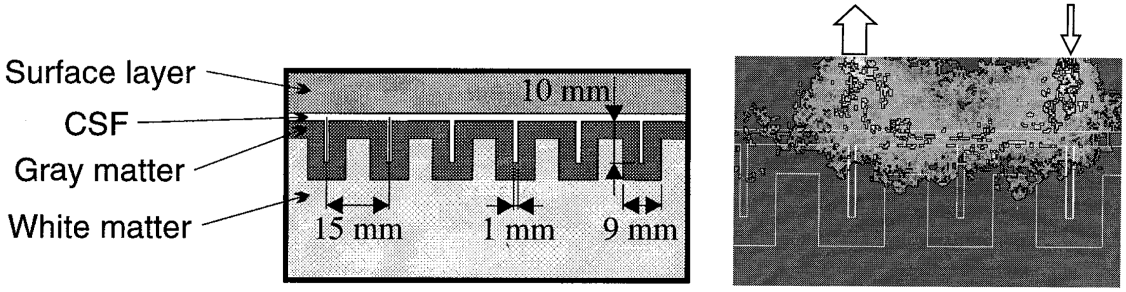

Figure 2.8: Model and spatial sensitivity profile for a source-detection distance of 30mm, fig. taken from [31].

They found that

- at small detection positions ($\leq 15\,mm$), the mean optical path length is approximately equal to the partial mean optical path length of the surface layer (skin, skull) resulting in the spatial sensitivity profile being confined to this surface layer.
- at intermediate positions ($\geq 15\,mm, \leq 25\,mm$), the partial mean optical path lengths of both cerebrospinal fluid (CSF) and gray matter (GM) layers increase with detection position.
- at large detection positions ($\geq 25\,mm$), the partial mean optical path lengths of surface and GM layers remain approximately constant while that of the CSF layer increases with source-detector spacing.

They concluded that for a source-detector spacing of 50mm, light spends approximately 65% of its path in scalp and skull, approximately 35% in the CSF and only approximately 5% in the gray matter of the cortex. Nevertheless, the contribution of the gray matter layer was estimated to be at least 20-30% of the absorption change in the NIRS signal.
In literature, commonly used source-detector distances resulting in a clear brain activity signal are between $3 - 4\,cm$ with the rule of thumb for frequency domain and continuous measurements that the depth of maximum brain sensitivity is approximately half the source-detector separation distance [13].

2.5 Review of existing fNIRS Technology

As a preparation for the CW fNIRS system design, the literature on NIRS instrument development approaches was reviewed. Tab. A.1 and A.2 (see Appendix A) summarize some of the important and comparable features of instruments developed by work groups around the world.
As can be seen, almost all instruments are based on CW technology, about two-thirds using lock-in approaches for improvement of the signal-to-noise ratio [18–20, 30, 44, 45, 48–53]. While some instruments use Time-Division Multiplexing (TDM) techniques, activating only one NIRS channel at a time [15, 32, 38, 45, 49, 52–55], others use frequency-encoded simultaneous emission and band-pass filter extraction or software based demodulation schemes [19], enabling the continuous measurement of all channels.