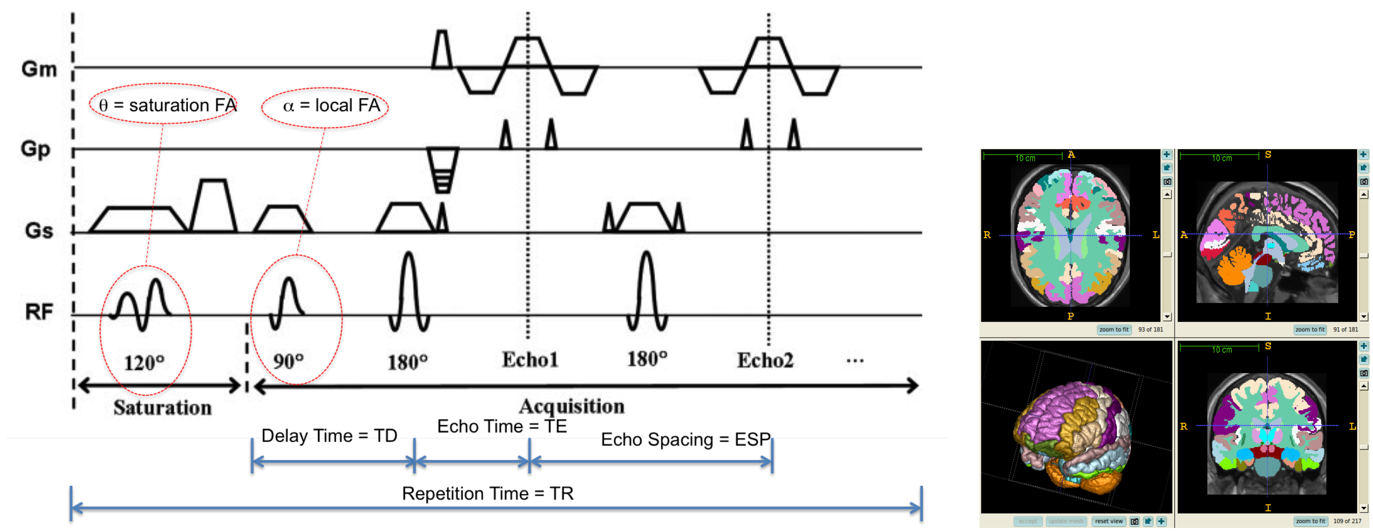
Advanced Applications of Synthetic MR and MAGiC

May 18, 2016

1 Problem Statement

Consider a magnetization signal M_{TD} that is defined as as function of **acquisition parameters** $\mathcal{K} = \{T_R, T_D, \theta, T_E, \alpha\}$ (@kenphwang are we considering α a control parameter?) and **tissue properties** $\mathcal{P} \equiv \{T_1, T_2, M_0\}$.



(a) (b)

Figure 1: (a) Synthetic MR Pulse sequence. (b) Neuroimaging basis.

$$M_{TD}(\mathcal{K}, \mathcal{P}, \mathbf{x}) = \left(M_0(\mathbf{x}) \frac{1 - (1 - \cos\theta) e^{-\frac{T_D}{T_1(\mathbf{x})}} - \cos\theta e^{-\frac{T_D}{T_1(\mathbf{x})}}}{1 - \cos\theta e^{-\frac{T_R}{T_1(\mathbf{x})}} cos\alpha} \right) e^{-\frac{T_E}{T_2(\mathbf{x})}} \quad (1)$$

Here, M_0 is the unsaturated magnetization, θ represents the *saturation* flip angle, and T_R and T_E denote repetition time and echo time, respectively. Parameters T_1 and T_2 represents relaxation times, and α is the *local* excitation flip angle. In general, excitation pulse α is a function of flip angle, i.e. $\alpha = \alpha(\theta)$ (@kenphwang why is this?). Note that the unsaturated magnetization M_0, along with relaxation times T_1 and T_2, are a function of spatial coordination $\mathbf{x}$. Basis functions ϕ_i represent the neuro anatomy. For completeness, consider $\phi_1 = \phi_{\text{gm}}$, $\phi_2 = \phi_{\text{wm}}$, $\phi_3 = \phi_{\text{csf}}$, $\phi_4 = \phi_{\text{tumor}}$ as a simplified set of the regions illustrated in Figure 1(b).

$$T_1(\mathbf{x}) = \sum_{i=1}^{N=4} T1_i \phi_i(\mathbf{x}) \qquad T_2(\mathbf{x}) = \sum_{i=1}^{N=4} T2_i \phi_i(\mathbf{x}) \qquad M_0(\mathbf{x}) = \sum_{i=1}^{N=4} M0_i \phi_i(\mathbf{x})$$

$$\bigcup_{i=1}^{N=4} \Omega_i = \Omega \qquad \Omega_n \cap \Omega_m = \varnothing \qquad \phi_i(\mathbf{x}) = \begin{cases} 1 & x \in \Omega_i \\ 0 & \text{otherwise} \end{cases}$$

Assume that the signal model for M_{TD} (1) is our measurment model in **image space** and is polluted with a white noise ν (with mean zero and variance $\mathbf{R}$). Hence, Eq. (1) can be written as:

$$z(\mathcal{K},\mathcal{P}) = \underbrace{M_{TD}(\mathcal{K},\mathcal{P},\mathbf{x})}_{h(\mathcal{K},\mathcal{P})} + \nu \tag{2}$$

Note that the observation z is a function of control parameters $\mathcal{K}$ and parameters of interest $\mathcal{P}$. The ultimate goal is to provide accurate estimate of the parameters $\mathcal{P}$, given some measurements z. Precise estimation of parameters $\mathcal{P}$ crucially depends on the values of control parameters $\mathcal{K} = \{T_R, T_D, \theta, T_E\}$. In other words, to ensure performance of the estimation algorithm, one needs to select the control parameters $\mathcal{K} = \{T_R, T_D, \theta, T_E\}$ such that the observation z provides useful information about the parameters $\mathcal{P}$. This is achieved my maximizing the mutual information between the control parameters $\mathcal{K}$ and parameters of interest $\mathcal{P}$. Within this framework we will consider the tissue properties to be normally distributed Gaussian parameters.

$\mathrm{T1}_{\mathrm{WM}} = \mathcal{N}(100ms, 20ms)$ $\mathrm{T1}_{\mathrm{GM}} = \mathcal{N}(120ms, 20ms)$ $\mathrm{T1}_{\mathrm{CSF}} = \mathcal{N}(320ms, 20ms)$ $\mathrm{T1}_{\mathrm{Tumor}} = \mathcal{N}(300ms, 20ms)$

$\mathrm{T2}_{\mathrm{WM}} = \mathcal{N}(100ms, 20ms)$ $\mathrm{T2}_{\mathrm{GM}} = \mathcal{N}(120ms, 20ms)$ $\mathrm{T2}_{\mathrm{CSF}} = \mathcal{N}(320ms, 20ms)$ $\mathrm{T2}_{\mathrm{Tumor}} = \mathcal{N}(300ms, 20ms)$

$\mathrm{M0}_{\mathrm{WM}} = \mathcal{N}(100??, 20??)$ $\mathrm{M0}_{\mathrm{GM}} = \mathcal{N}(120??, 20??)$ $\mathrm{M0}_{\mathrm{CSF}} = \mathcal{N}(320??, 20??)$ $\mathrm{M0}_{\mathrm{Tumor}} = \mathcal{N}(300??, 20??)$

2 WIP - Optimal Experimental Design

As discussed before, performance of estimation process crucially depends on the value of control parameters $\mathcal{K}$. Hence, it is important to develop mathematical tools to identify the control parameters $\mathcal{K}$ such that they provide the best observation data for accurate estimation of parameter $\mathcal{P}$. This is equivalent with maximizing the mutual information between the observation data and parameters $\mathcal{P}$. Based on information theory, mutual information is defined as the reduction of uncertainty in one parameter due to knowledge of the other parameter.

$$I(\mathcal{P}; z) = \int_z \int_p p(\mathcal{P}, z) \ln\left(\frac{p(\mathcal{P}, z)}{p(\mathcal{P})p(z)}\right) d\mathcal{P}dz \tag{3}$$

We make use of Bayes theorem to simplify the above equation. By substituting $p(\mathcal{P}, z)$ with $p(z|\mathcal{P})p(\mathcal{P})$, Eq. (3) can be written as:

$$I(\mathcal{P}; z) = \int_z \int_p p(z|\mathcal{P})p(\mathcal{P}) \ln\left(\frac{p(z|\mathcal{P})p(\mathcal{P})}{p(\mathcal{P})p(z)}\right) d\mathcal{P}dz \tag{4}$$

Or,

$$I(\mathcal{P}; z) = \int_z \int_p p(z|\mathcal{P})p(\mathcal{P}) \ln\left[p(z|\mathcal{P})\right] d\mathcal{P}dz - \int_z p(z)\ln p(z) dz \tag{5}$$

Note that due to dependence of observation data z on control parameters, the mutual information $I(\mathcal{P}; z)$ is a function of control parameter $\mathcal{K}$. In order to maximize the reduction of uncertainty in parameter estimate (i.e. to have the most confident estimates of the parameter $\mathcal{P}$), one can simply maximize the mutual information between the observation data and parameters of interest:

$$\max_{\mathcal{K}} I(\mathcal{P}; z) \tag{6}$$

The above maximization results in *optimal* values of control parameter $\mathcal{K}$ for accurate estimation of parameter $\mathcal{P}$. Note that in Eq. (5), $p(z|\mathcal{P})$ is defined as a Gaussian distribution with mean $h(\mathcal{K}, \mathcal{P})$ and variance $\mathbf{R}$. As well, $p(\mathcal{P})$ denotes the prior distribution of parameter $\mathcal{P}$, which for the ease of calculations, is considered to be a Gaussian distribution with some prior mean $\hat{\mathcal{P}}^-$ and prior covariance Σ^-, i.e. $p(\mathcal{P}) \sim \mathcal{N}(\hat{p}^-, \Sigma^-)$. Method of quadrature points can be used to evaluate Eq. (5).

We emphasize here that the mutual information will be the same on different pixels with the same tissue types. This is due to the similarities in statistics of $\mathcal{P}$ between the two different pixels with the same tissue properties. In other words, whenever two different pixels have the same tissue properties, then the distribution of parameter $\mathcal{P}$, denoted by $p(\mathcal{P})$, is the same and so is the value of mutual information. Hence, there is no need to evaluate the mutual information for each pixel in a region with the same tissue type.

On the other hand, in a case that the tissue properties for each pixel are different from the other, then the mutual information needs to be evaluated for each and every pixel of interest.

3 WIP - Model Data Fusion

After finding the optimal values of the control parameter $\mathcal{K}$, we can proceed and perform the model-data fusion to get a better understanding about the uncertainties involved in parameters $\mathcal{P}$. The fusion of observational data with mathematical model predictions promises to provide greater understanding of physical phenomenon than either approach alone can achieve. In here, a minimum variance framework is being used for model - data fusion. Based on minimum variance technique, posterior statistics of parameter $\mathcal{P}$ can be written as:

$$\hat{\mathcal{P}}^{+} = \hat{\mathcal{P}}^{-} + \mathbf{K}[z - \underbrace{\mathcal{E}^{-}[h(\mathcal{K},\mathcal{P})]}_{h^{-}}] \tag{7}$$

$$\Sigma^{+} = \Sigma^{-} + \mathbf{K}\Sigma_{hh}\mathbf{K}^{T} \tag{8}$$

where, the gain matrix K is given by

$$\mathbf{K} = \Sigma_{\mathcal{P}z}\left(\Sigma_{hh}^{-} + \mathbf{R}\right)^{-1} \tag{9}$$

Here, $\hat{\mathcal{P}}^{-}$ and $\hat{p}^{+}$ represent prior and posterior values of the mean for parameter vector $\mathcal{P}$, respectively:

$$\hat{\mathcal{P}}^{-} \equiv \mathcal{E}^{-}[\mathcal{P}] = \int \mathcal{P}^{-}p(\mathcal{P})d\mathcal{P}\hat{\mathcal{P}}^{+} \equiv \mathcal{E}^{+}[\mathcal{P}] = \int \mathcal{P}^{+}p(\mathcal{P})d\mathcal{P} \tag{10}$$

where, $p(\mathcal{P})$ denotes the probability density function of parameter $\mathcal{P}$. Similarly, the prior and posterior covariance matrices Σ^{-} and σ^{+} can be written as:

$$\Sigma^{-} \equiv \mathcal{E}[(\mathcal{P} - \hat{\mathcal{P}}^{-})(\mathcal{P} - \hat{\mathcal{P}}^{-})^{T}] \tag{11}$$

$$\Sigma^{+} \equiv \mathcal{E}[(\mathcal{P} - \hat{\mathcal{P}}^{+})(\mathcal{P} - \hat{\mathcal{P}}^{+})^{T}] \tag{12}$$

The matrices $\Sigma_{\mathcal{P}z}$ amd Σ_{hh} are defined as:

$$\Sigma_{\mathcal{P}z} \equiv \mathcal{E}[(\mathcal{P} - \hat{\mathcal{P}})(h - \hat{h}^{-})^{T}] \tag{13}$$

$$\Sigma_{hh} \equiv \mathcal{E}[(h - \hat{h}^{-})(h - \hat{h}^{-})^{T}] \tag{14}$$

Eq. (7) along with Eq. (8) provide posterior mean and covariance of parameter $\mathcal{P}$ given observation data $\tilde{z}$ and model predictions $h(\mathcal{K},\mathcal{P})$. We emphasize here that the optimal values of $\mathcal{K}$, obtained from Eq. (6), are used in Eq. (7).

4 WIP - Overall Picture

The following diagram illustrates the general work-flow of the process:

5 WIP - T1, T2, M0 Reconstruction

Given the image space date for multiple acquistion parameters $\{M_{TD}(\mathcal{K}_1), M_{TD}(\mathcal{K}_2), M_{TD}(\mathcal{K}_2), ...\}$, $\mathcal{K}_i = \{T_{R_i}, T_{D_i}, \theta_i, T_{E_i}, \alpha_i\}$ (@kenphwang 2 delay times and 4 echoes correct?),

The reconstruction algorithms for T1, T2, M0 is as follows:

- (@kenphwang can we get the current code for this recon.)
- (@kenphwang Can you provide an example data set ? is this real/imaginary data? or magnitude only? is α, θ fixed?)
-

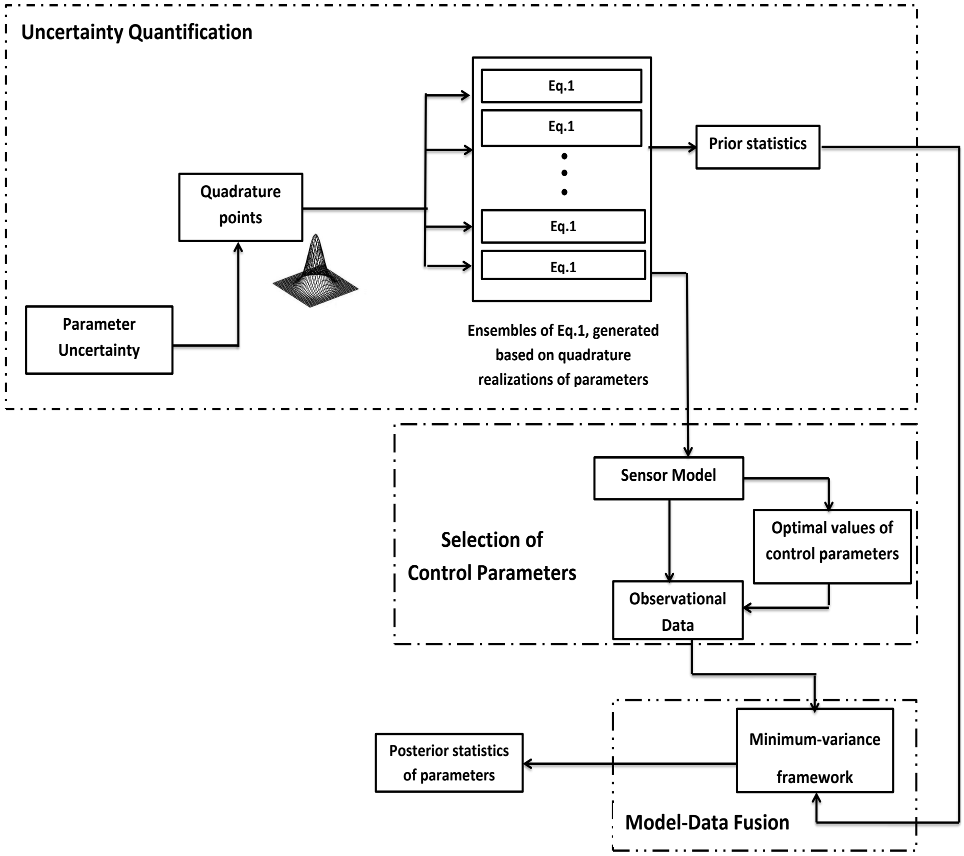


Figure 2: Schematic view of the estimation process

6 WIP - Physics Model

The steady-state magnetization M_{TD} at a specific delay time T_D can be found as a function of flip angle θ, repetition time T_R, excitation pulse α, and relaxation time T_1:

$$M_{TD} = M_0 \frac{1 - (1 - \cos(\theta))e^{-\frac{T_D}{T_1}} - \cos(\theta)e^{-\frac{T_R}{T_1}}}{1 - \cos(\theta)e^{-\frac{T_R}{T_1}} \cos(\alpha)}$$

where, M_0 is the unsatuarated magnetization.

7 WIP - Mathematical Framework

The underlying philosophy and assumptions within our approach is that the physics models are 1st order accurate or within 70-80% of the needed accuracy and the error is adequate within the assumed Gaussian noise. Gaussian distributions provide analytical representations of the random variables of interest (ie T1, T2) within the Bayesian setting and provide a crux for understanding. In particular, we say that a random variable η belongs to a multi-variate normal distribution of mean $\mu \in \mathbb{R}^n$ and covariance $\Sigma \in \mathbb{R}^{n \times n}$

$$\eta \sim \mathcal{N}(\mu, \Sigma) \Rightarrow p(\eta) = \frac{1}{2\,\pi\, \det \Sigma} \exp\left(-\frac{1}{2}\|\mu - \eta\|^2_\Sigma\right)$$

1. Our data acquistion model, $\mathcal{G}(\vec{k}, \theta) : \mathbb{R}^a \times \mathbb{R}^m \rightarrow \mathbb{R}^n$, maps deterministic acquisition parameters, $\vec{k} \in \mathbb{R}^a$, and uncertain parameters, $\theta \in \mathbb{R}^m$ to observables, $\vec{z} \in \mathbb{R}^n$ (or $\vec{z} \in \mathbb{C}^n$). Explicitly, we will assume that the

measurement models are corrupted by zero mean white noise noise of a **known** covariance matrix, $\Sigma_z \in \mathbb{R}^{n\times n}$

$$
\begin{aligned}
\vec{z} &= \mathcal{G}(\vec{k};\theta) + \eta \qquad \eta \sim \mathcal{N}(0,\Sigma_z)\\
\vec{k} &= (\text{TE, TR, etc})\\
\theta &= (\text{T1, T2, etc})
\end{aligned} \tag{15}
$$

η may be interpreted as the measurement noise or the acquisition noise in the sensor model. For a deterministic measurement model $\mathcal{G}$, the conditional probablity distribution has an explicit analytical form and may be written as a **known** Gaussian distribution.

$$
p(\vec{z}|\theta) = \mathcal{N}(\mathcal{G}(\vec{k};\theta),\Sigma_z)
$$

2. Additional **known** information is the prior probability distributions for the model parameters, $p(\theta)$. For simplicity, assume that Prior parameters are Gaussian distributed of **known** mean, $\hat{\theta}$ and covariance, Σ_θ

$$
\theta \sim \mathcal{N}(\hat{\theta},\Sigma_\theta)
$$

3. Bayes theorem is fundamental to the approach. The probability of the measurements $p(z)$ must be interprited in terms of the known information. The probability of the measurements may be derived from the marginalization of the joint probability and has the interpretation as the projection of the joint probability onto the measurement axis.

$$
p(z) = \int_\theta p(\theta,z)\; d\theta = \int_\theta p(z|\theta)\; p(\theta)\; d\theta
$$

4. The concept of informational entropy [Madankan et al., 2015], $H(Z)$, provides a mathematically rigorous framework to look for measurement acquisition parameters, $\vec{k}$, with the high information content of the reconstruction. Given a probability space $(\Omega,\mathcal{F},p)$ (probability maps from the sigma-algebra of possible events $p:\mathcal{F}\to[0,1]$ sigma-algebra, $\mathcal{F}$, defined on set of 'outcomes' Ω [Durrett, 2010]), we will define information of an event as proportional to the inverse probability.

$$
\text{information} \equiv \frac{1}{p(z)}
$$

Intuitively, when a low probability event occurs this provides high information. The informational entropy is an *average* of the information content for a sigma algebra of events $\mathcal{F}$

$$
H(Z) = \int_Z p(z)\ln\frac{1}{p(z)}\; dz \qquad p(z) = \int_\theta p(z|\theta)\; p(\theta)\; d\theta
$$

Hence this entropy measure is an average of the information content for a given set of events, $\mathcal{F}$, and is proportional to the variance or uncertainty in which the set of events occur. This agrees with thermodynamic entropy; if the information containing events are completely spread out such as in a uniform distribution, the entropy is maxmized. The entropy is zero for a probability distribution in which only one event occurs. Zero information is gained when the same event always occurs ($0\ln\frac{1}{0}=0$). Intuitively, we want to find acquisition parameters, $\vec{k}$, for which the measurements are most uncertain

$$
\max_k H(Z) \quad \Leftrightarrow \quad \min_k \int_Z dz \underbrace{\int_\theta d\theta\; p(z|\theta)\; p(\theta)}_{p(z)} \underbrace{ln\left(\int_\theta d\theta\; p(z|\theta)\; p(\theta)\right)}_{ln\; p(z)}
$$

Alternatively we may consider this entropy maximization problem as a sensitivity analysis for the variance of the measurement Z, ie . $\max_k H(Z) \approx \max_k \text{Var}(Z)$

$$
\bar{Z} = \mathbb{E}[Z] = \int_Z dz\; z \underbrace{\int_\theta d\theta\; p(z|\theta)\; p(\theta)}_{p(z)}
$$

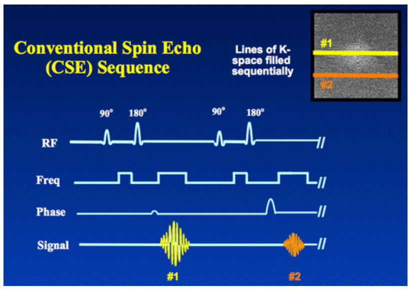
$$
\begin{aligned}
\mathbb{E}[(Z-\bar{Z})^2] &= \int_Z dz\; (z-\bar{Z})^2 \underbrace{\int_\theta d\theta\; p(z|\theta)\; p(\theta)}_{p(z)}\\
&\propto \int_Z dz\; (z-\bar{z})^2 \int_\theta d\theta \exp\left(-\frac{1}{2}\|z-\mathcal{G}(\vec{k},\theta)\|^2_{\Sigma_z}\right)\exp\left(-\frac{1}{2}\|\theta-\hat{\theta}\|^2_{\Sigma_\theta}\right)
\end{aligned}
$$

Probilistic integrals may be computed from uncertainty quantification techniques [Fahrenholtz et al., 2013].

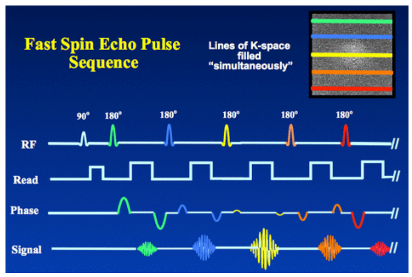
8 WIP - Echo train length

In conventional spin-echo imaging, two basic timing parameters are required, repetition time (TR) and echo time (TE), Figure 3(a). Similar to fast spin echo (FSE) imaging, the acquistion is setup to acquire multiple lines of k-space in a single TR. In this situation, TE is replaced by effective echo time and addition parameters are needed:

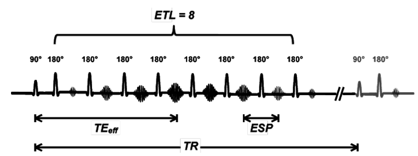
- $\mathrm{TE}_{\mathrm{eff}} \equiv$ the time at which the central lines of k-space are being filled.
- Number of echoes $\equiv$ called echo train length (ETL)
- Time between echoes $\equiv$ called echo spacing (ESP)



(a)



(b)



(c)

Figure 3: (a)

TODO - need to update signal model for multiple read out lines

9 WIP - Inverse Problem Framework

$$\vec{z} = \mathcal{G}(\theta) + \eta \qquad \eta \sim \mathcal{N}(0, \Sigma_z)$$
$$p(z|\theta) = \exp\left(\|\vec{z} - \mathcal{G}(\theta)\|^2_{\Sigma_z}\right)$$
$$d\left(\vec{z}, \mathcal{G}(\theta^*)\right) = \min_{\theta \in \Omega} d\left(\vec{z}, \mathcal{G}(\theta)\right) \qquad \theta = (\mu_{\mathrm{CSF}}, \mu_{\mathrm{GM}}, \mu_{\mathrm{WM}}, \mu_{\mathrm{Tumor}})$$

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A Bayes - An intuitive example

Bayes theorem is fundamental to the approach and is immediately follows from the definition of conditional probability

$$\left.\begin{aligned} p(y|x) &\equiv \frac{p(x,y)}{p(x)} \\ p(x|y) &\equiv \frac{p(x,y)}{p(y)} \end{aligned}\right\} \Rightarrow p(y|x)p(x) = p(x,y) = p(x|y)p(y) \Rightarrow \qquad \begin{aligned} p(y|x) &= \frac{p(x|y)p(y)}{p(x)} \\ p(x|y) &= \frac{p(y|x)p(x)}{p(y)} \end{aligned}$$

As a concrete example, consider the explicit two dimensional joint Gaussian distribution as a medium for understanding. Here we have two random variables $\mathbf{x}_1$ and $\mathbf{x}_2$ defined on the same probability space, Ω.

$$\mathbf{x}_i : \Omega \to \mathbb{R} \qquad P\left(\{\omega : \mathbf{x}_i(\omega) \in A\}\right) = \int_A p(\eta_i) d\eta_i$$

Intuitively, if we are **given** the joint distribution, $p(\eta_1, \eta_2)$, knowledge of the realization of one particular random variable provides information on the realization of the second random variable.

$$p(\eta_1, \eta_2) = \frac{1}{2\,\pi\,\sqrt{\det \Sigma}} \exp\left(\frac{1}{2} \begin{bmatrix} \eta_1 - \mu_1 \\ \eta_2 - \mu_2 \end{bmatrix}^\top \underbrace{\begin{bmatrix} \sigma_1^2 & r_{12}\sigma_1\sigma_2 \\ r_{12}\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}}_{\equiv \Sigma} \begin{bmatrix} \eta_1 - \mu_1 \\ \eta_2 - \mu_2 \end{bmatrix} \right)$$

See [**?**] (Sec 3.10), characteristic functions are used to show that individual marginal densities of joint Gaussian random variable is also Gaussian.

$$p(\eta_1) = \int_{\eta_2} p(\eta_1, \eta_2)\; d\eta_2 = \frac{1}{\sqrt{2\,\pi\,\sigma_2^2}} \exp\left(-\frac{(\eta_1 - \mu_1)^2}{2\sigma_1^2} \right)$$

$$p(\eta_2) = \int_{\eta_1} p(\eta_2, \eta_1)\; d\eta_1 = \frac{1}{\sqrt{2\,\pi\,\sigma_1^2}} \exp\left(-\frac{(\eta_2 - \mu_2)^2}{2\sigma_2^2} \right)$$

Conditional probablity is *defined* through the algegraic reduction of the ratio of the joint and the marginal densities

$$p(\eta_1|\eta_2) = \frac{p(\eta_1, \eta_2)}{p(\eta_2)} = \frac{1}{\sqrt{2\,\pi\,\sigma_{1|2}^2}} \exp\left(-\frac{(\eta_1 - \mu_{1|2})^2}{2\sigma_{1|2}^2} \right) = \frac{p(\eta_1)}{p(\eta_2)} \frac{1}{\sqrt{2\,\pi\,\sigma_{2|1}^2}} \exp\left(-\frac{(\eta_2 - \mu_{2|1})^2}{2\sigma_{2|1}^2} \right)$$

$$\mu_{1|2} = \mu_1 - \frac{r_{12}\sigma_1\sigma_2}{\sigma_2^2}(\eta_2 - \mu_2) \qquad \sigma_{1|2} = \sigma_1^2 - \frac{(r_{12}\sigma_1\sigma_2)^2}{\sigma_2^2}$$

$$\mu_{2|1} = \mu_2 - \frac{r_{12}\sigma_1\sigma_2}{\sigma_1^2}(\eta_1 - \mu_1) \qquad \sigma_{2|1} = \sigma_2^2 - \frac{(r_{12}\sigma_1\sigma_2)^2}{\sigma_1^2}$$