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BME 4420/7450
Final Exam—Fall 2022
Due by Tuesday, Dec 13, at 11:59pm.

1. Briefly explain how each of the following operations would affect image quality (15 points).

a. Multiplying all pixel intensities by 10.

Answer:

Multiplying all pixels with the same factor doesn't change the SNR. Hence the image quality won't be improved.

b. Averaging pixel intensities over a 3x3 neighborhood. This produces an image with pixel intensity at each position (x,y) equal to the average intensity in a region in the original image defined by {(x+i, y+j), where $|i|, |j| \leq 1$*}.*

Answer:

Averaging pixel intensities over a 3X3 neighborhood act as a smoothing filter. So, the image becomes less noisy. However, this operation will blur the image.

c. Using linear interpolation to halve the pixel size in both x and y, and hence double the image size (e.g., from 256x256 to 512x512).

Answer:

In this case, the resolution of the image would be better because of the increase in number of pixels. This will improve the spatial resolution.

2. Define the following terms and briefly explain how they are measured and why they are useful (20 points):

a. NMR relaxation times (T_1 and T_2)

Answer:

In equilibrium, the net magnetization M_0 is in the Z-direction and there is net magnetization in X and Y-direction (M_{XY}=0). When a time varying field is applied, the net magnetization shifts in the transverse direction. Over time, spin orientations become randomized again. Hence, the transverse magnetization decreases (transverse relaxation) and longitudinal magnetization recovers (longitudinal relaxation) again.

The time constant for transverse relaxation is called T2. To measure T2, after tipping the net magnetization with a 90° pulse, we need to acquire a series of images, each at a different time point. Then, if we plot transverse magnetization over M_0 (M_{XY}/M_0) vs time, we will get an exponentially decaying line.

$$M_{XY}(t) = M_{XY}(0) * e^{-t/T2}$$

$$\text{Or, } \ln(M_{XY}(t)) = \ln(M_{XY}(0)) - t/T_2$$

$$\text{Or, } y = c + mx$$

So, we can fit this to a straight line and find the slope of this line. From the slope we can measure T_2 as T_2=-1/slope.
On the other hand, the time constant for longitudinal relaxation is called T_1. To measure T_1, we apply an 'inversion' B_1 pulse to orient M (magnetic moment per unit volume) -Z axis. Then, we need to wait some time, TI (inversion time) during which M_z recovers towards M_0. After that, we tip spins into a transverse plane and measure the magnetization immediately. If we plot M_z vs time, we get an exponentially growing graph.

$$M_z(TI) = M_0*(1-2e^{-TI/T2})$$

$$\text{Or, } TI/T_1 = - \ln(0.5*(1- M_z(TI)/M_0))$$

$$\text{Or, } mx = y;$$

We again fit it to a straight line, and 1/slope gives us the T_1.
T_1 and T_2 values are the main sources of contrast in MR image. Different tissues have different T_1 and T_2 values, and depending on the difference between them we can create a T_1 weighted or T_2 weighted image. We can also use contrast agent to modulate these values and create contrast between the tissue we want to study and background.

b. Diffusion anisotropy

Answer:

Usually molecular displacement is isotropic (no preferred direction) in a sloution. However, displacement of water molecule in tissue is anisotropic constrained by cell membranes. Hence, the largest displacements are parallel to axons in brain. This is known as diffusion anisotropy. Thus, variation of displacements over orientations reflects membrane density, membrane permeability, fiber coherence. Diffusion anisotropy maps can reveal structure within white matter.

Measurement: We know that spin precess around a magnetic field, B_{loc} and rate of precession is proportional to B_{loc}. Hence, we can use the precession frequency to determine spin position and by using changes in frequency, we can detect changes in position. For this, we use gradient pulse sequence. We measure the molecule's position at first field gradient pulse. Then, we reverse the gradient field by applying a second pulse and corresponding position is measured. Here the residual phase is proportional to displacement. Here, signal depends on the spin displacements; diffusion attenuates the signal.

$$S=S_0*e^{-b/D}$$

$$\text{Or, } \ln(S)= -b/D + \ln(S_0)$$

Where, b is the displacement and $D = \langle r^2 \rangle/2T$

Usage:

- reveals tissue microstructure
- detects stroke
- do fiber tracking

c. Perfusion

Answer:

Perfusion refers to the volume of blood delivered (only to capillary) to a volume of tissue per unit time.

Perfusion can be measured via injecting a contrast agent and measuring signal change in tissue of interest. Then, we plot the 'time-activity' curve from which perfusion can be measured from the initial slope since slope = perfusion*arterial concentration of contrast agent.

Perfusion is useful because it reflects cardiac output, vascular system conductance, tissue metabolism.

d. Partition coefficient (λ)—also known as the distribution volume of a tracer

Answer:

In tracer-based perfusion measurement, if the arterial input of tracer is constant, i.e., $C_A(t)=C_A$, tissue tracer concentration reaches an equilibrium value as described by the following equation, $C_T(\infty)= \lambda * C_A$, where the proportionality constant λ is called partition coefficient.

λ can also be measured in a similar way as perfusion. By injecting a tracer and measuring the signal change in tissue of interest. If t is long enough, C_T will reach a steady state. Now, from the 'time-activity' curve, we can measure λ as the plateau region's value = $\lambda * C_A$.

λ is very important to measure the mean transit time or clearance time which is important in knowing how acute a stroke is. We also get to measure perfusion via utilizing λ.

3. Medical imaging techniques typically have a spatial resolution on the order of millimeters. Explain how it is possible to use these methods to gain information about tissue constituents at much smaller length scales, for example on the molecular (10^{-6} mm), cellular (~10^{-3} mm) and capillary (~10^{-2} mm) scales. For each of these length scales, include an example from ultrasound, CT, PET or MRI. (15 points)

Answer:

For molecular level imaging, PET is the most suitable modality. In PET, we can use radionuclide that binds to particular molecule and gives us information about that molecule. For example, fluoro-deoxy-glucose (FDG) is a glucose analogue that accumulates in proportion to glucose concentration. Via PET imaging, we can see that distribution of FDG indication metabolic rate. From this information, we can infer about the tumor growth.

Diffusion Tensor Imaging (DTI) a form of MRI can be used for cellular level information. For example, we know that water molecules exhibit anisotropic diffusion in the brain showing largest displacements along the axon of the neurons. Using this information, we can infer about the cellular level microstructure, we can do fiber tracking, etc.

MRI imaging with contrast agent can be used for capillary level imaging. As discussed in the answer of question 2, when the contrast agent is injected in the blood, it gets distributed to interstitial space and tissue which disrupts the magnetization via increasing transverse relaxation rate, R_2. Hence, the signal intensity drops with time while difference in R_2 increases. From the difference in R_2 and time graph we can measure cerebral blood flow via capillary and detect stroke.

4. In an fMRI experiment, tissue T_2^* changes in voxels with increased neuronal activity (due to the BOLD effect). The signal intensity from a given voxel is

$$S = S_0 \cdot e^{-T_E/T_2^*} \qquad [1]$$

where T_E is the time (after spin excitation) at which the image data are acquired and T_2^* is the transverse relaxation time constant (including the dephasing effects of B_0 field inhomogeneities). The image contrast, ΔS, produced by the time-constant change, ΔT_2^*, is given by

$$\Delta S = \frac{dS}{dT_2^*} \cdot \Delta T_2^* .$$

The time T_E is an experimental parameter under your control. (20 points)

a. Use Eq. [1] to express ΔS as a function of T_E (as well as T_2^* and ΔT_2^*).

b. What value of T_E would you choose to maximize the BOLD contrast, ΔS, in your experiment?

c. Find an expression for the fractional signal change, $\Delta S/S$, under this optimal condition, in terms of ΔT_2^*.

d. In an fMRI experiment, $T_E = 50$ ms and $\Delta S/S = 1\%$ in the activated region (assume that T_E is optimized). What is the change in tissue T_2^* due to the BOLD effect in this case?

Answer:

a. Here, $S = S_0 . e^{-T_E/T_2^*}$ and

$$\Delta S = \frac{dS}{dT_2^*} \cdot \Delta T_2^*$$

$$= \frac{d}{dT_2^*}\left(S_0 . e^{-T_E/T_2^*}\right) . \Delta T_2^*$$

$$= S_0 . e^{-T_E/T_2^*} . (-T_E)\left(-\frac{1}{T_2^{*2}}\right) . \Delta T_2^*$$

$$\Rightarrow \Delta S = S_0 e^{-T_E/T_2^*} . \frac{\Delta T_2^*}{T_2^{*2}} . T_E \quad \text{——— (1)}$$

$$\Rightarrow \Delta S = S . \frac{\Delta T_2^*}{T_2^{*2}} . T_E \quad \text{——— (2)}$$

where only T_E can be changed. Hence, T_E is the variable.

b. for maximizing ΔS, in terms of T_E.

$$\frac{d}{dT_E}(\Delta S) = 0$$

$$\Rightarrow \frac{d}{dT_E}\left(S_0 e^{-T_E/T_2^*} . \frac{\Delta T_2^*}{T_2^{*2}} . T_E\right) = 0 \quad [\text{from (1)}]$$

$$\Rightarrow S_0 e^{-T_E/T_2^*} . \frac{\Delta T_2^*}{T_2^{*2}} + S_0 e^{-T_E/T_2^*} . \frac{\Delta T_2^*}{T_2^{*2}} . T_E . \left(-\frac{1}{T_2^*}\right) = 0$$

$$\Rightarrow S_0 e^{-T_E/T_2^*} . \frac{\Delta T_2^*}{T_2^{*2}} = S_0 e^{-T_E/T_2^*} \frac{\Delta T_2^*}{T_2^{*2}} . T_E . \frac{1}{T_2^*}$$

$$\Rightarrow 1 = \frac{T_E}{T_2^*}$$

$$\therefore T_E = T_2^*$$

So, for maximizing ΔS, the optimal value for T_E should be equal to T_2^*

c. From ②, $\frac{\Delta S}{S} = T_E \cdot \frac{\Delta T_2^*}{T_2^{*2}}$

$= T_E \cdot \frac{\Delta T_2^*}{T_E^2}$

$\therefore \frac{\Delta S}{S} = \frac{\Delta T_2^*}{T_E}$ ——— ③

d. Given, $T_E = 50$ ms

$\frac{\Delta S}{S} = 0.01$

from ③, $\Delta T_2^* = \frac{\Delta S}{S} \times T_E$

$= 0.01 \times 50$ ms

$= 0.5$ ms

So, the change in tissue T_2^* is 0.5 ms due to the BOLD effect.

5. The last image analysis project (Project 8) examined the binding of a radioactive tracer (fallypride) to the dopamine (D2) receptor. Suppose you want to evaluate a new drug that binds to and blocks the dopamine receptor—this is called a dopamine antagonist, because it blocks the action of dopamine (several antipsychotic medications are in this class of drugs). The new drug is not visible on PET scans. How could you use the radiotracer to determine how much of the new drug is binding to dopamine receptors? Outline the steps of your experiment, including image analysis. (10 points)

Answer:

I think we need to do two separate experiments to achieve our goal in this case. The steps are briefly explained below:

1. At first, we do the whole project just like the previously. We only introduce the radiotracer, look for its concentration in our region of interest and in a control region. We set up the logan plot and for each pixel value, we measure the slope. Thus, we get to see the regions where the radiotracer binds with the dopamine receptor.
2. Now, in the second experiment, we inject both the radiotracer and the new drug (same amount of molecule) into the blood.
3. In the first experiment, the basal ganglia (bg) region with dopamine receptors lights up well and we mark the region to create a mask for bg. However, in this case, both tracer and new drug will compete with each other to bind with the dopamine receptor. Some spots will be taken by the tracer and the remaining ones are where new drug is going to bind. Hence, bg region is not going to be very visible. So, we do image registration and take the same bg mask we created for the first experiment.
4. The rest of the steps are exactly the same. From logan plot, we create a DVR map.
5. Now, the DVR map from experiment 1 and 2 are going to be slightly different. DVR map of experiment 1 will have more bright pixels than the latter one. That's expected because some dopamine receptors were taken up by the drug that is not visible to the PET scan.
6. Although we can not exactly measure how much new drug could bind with receptors, we will get a map to see where the drug bound with receptors. These are the pixels that had high intensities in the first DVR map, but low intensities in the second DVR map.

6. Suppose you are hired to analyze signal changes in an fMRI brain activation experiment. You find that there is a strong variation in signal around 0.2 Hz, and you suspect this is due to respiratory motion of the chest wall (which slightly changes the B_0 magnetic field in the head). (20 points total)

a). You decide to try to filter out the respiratory signal changes, assuming a respiratory rate of 0.2 Hz. Why would this improve the sensitivity of the fMRI experiment? Describe the steps you would use to do this.

Answer:

First, a power spectrum analysis (Fourier Transform) should be done to see the effect of all the frequencies available in the signal. If we just want to remove the 0.2 Hz frequency component, then, using a simple notch filter or band stop filter would be enough. Now, this removal of unnecessary component distributes the power to the necessary frequency region better. Hence, the sensitivity improves due to increase in SNR.

b). Although the filtering method above improves the data, you are not completely satisfied with the results. You take a deep breath and think about what to do next. In a flash of insight, you realize that respiration is not perfectly periodic, and some inhalation/exhalation cycles are significantly longer or shorter than the mean, which implies that the respiratory spectrum is probably not a single, narrow peak with fixed frequency during the entire experiment. Fortunately, someone on the team recorded the circumference of the subject's chest (call this variable s) as a function of time during the experiment (this was measured with a stretch-sensitive belt around the subject's chest). You decide to use the measurements of s to improve your estimates of brain activation signal changes. As a first step, you develop a model of how signal intensity in the brain is related to s. Let the signal intensity of the pixel in row i and column j be written I(i, j), You choose a polynomial to model the influence of s on I(i,j):

$$I(i,j) = a_0 + a_1 s + a_2 s^2 + \cdots$$

Describe how you would determine the coefficients a_i. Are these likely to have the same values in all pixels?

Answer:

For this we need images at few time points. Now, for each time point, we get an intensity and s value. So, we can create the equation as mentioned in the question. Now, for, let's say n time points, we will get a system of equation (n equations). If number of unknown coefficients is also n or less than n, then we can solve the equations and determine the values for a_i. And, these values will be different for different pixels.

c). Describe the steps you would use to analyze the fMRI data, including the approach of part 'b'. This should be a (brief) set of procedures, but similar in outline to those of the analysis projects you've done in this course. You don't have to include MATLAB commands but should summarize each conceptual step.

Answer:

- ✓ Preprocessing to remove spurious signal variation
    - Correcting head motion through suitable registration methods like rotation, translation, intensity scaling.

- Removing respiration and heart beat related components from the signal via using band stop filtering, local averaging, etc.
- Removing instrument drift via fitting a linear or non-linear line to the drift and subtracting it from the signal.

✓ Measuring the activation signal
- Creating a function that has the expected time dependence of the activation signal
  Y(t) = r(t) + e(t)
  Here, r(t) is the function mentioned in b. $r(t) = a_0 + a_1 s + a_2 s^2 + \cdots$
  and e(t) is fMRI related activation function.
  [Reference: Agrawal, Uday, Emery N. Brown, and Laura D. Lewis. "Model-based physiological noise removal in fast fMRI." *Neuroimage* 205 (2020): 116231.]
- Finding the image intensity in a pixel as a function of time
- Evaluating the fit and make it better.
- Repeating the same strategy for all pixels
- Displaying the results as a statistical map

✓ Statistical testing to judge the significance of signal changes
- Using statistical measures (correlation coefficient, student's t-statistic) of the size of the signal difference relative to the noise

✓ Displaying activation map
- Thresholding the statistical map at some level of significance
- Displaying map (in color) overlaid on anatomical image or 3D volume

Please sign the following Honor code statement:
I have not given or received help on this examination that in any way conflicts with the Vanderbilt University honor code.

Signed: Rana Mozumder Date: 12/12/2022