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Quantifying Enlargement of Brain Cerebrospinal Fluid Spaces: A Differential Equation Approach to Clinical Outcome in Melancholia

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Abstract

The physiological processes involved in cognitive neurology are highly complex, spanning a wide range of inter-related temporal and spatial scales. Experiments demonstrate that the level of measured brain activity increases with an increase in cognitive load, with observations including linear and non-linear neural cognitive relationships [1]. Mathematical and computational modeling approaches have been applied to different aspects neurosciences, starting from cysts and tumour-like lesions to metastasis and treatment response [2]. The complexity of relationship between brain cerebrospinal fluid (CSF) space changes and patient prognosis in melancholic depression is well suited to quantitative approaches as it provides challenges and opportunities for new developments.

The purpose of this article is to come up with present mathematical trends in the clinical outcome of depressive patients. To be more specific, we focus on mathematical models that are capable of addressing critical questions associated with intra-cranial neoplasms and brain tumours, their growth and patient-specific differential diagnosis. Also, we establish the explicit interactions between the brain-delivered neurotrophic factor (BDNF) *Val66Met* gene and early-life stress (ELS) exposure in brain [3].

Keywords: *Neuroscience; Cognitive; Cerebrospinal Fluid (CSF); Cystic Lesion; Brain Tumour; Melancholia; Magnetic Resonance Imaging (MRI)*

Introduction

An important aspect in cognitive neuroscience is the understanding of how the brain responds to increasing levels of cognitive load and it has been shown by experiments that the level of measured brain activity does indeed increase as cognitive load increases with observations including linear and non-linear relationships. A basis to these theoretical models is the description of neural efficiency (the rate of increasing measures of brain activity with increasing cognitive load) and neural capacity (the maximal level of brain activity reached as cognitive load increases). The concepts of neural efficiency and capacity have been unified into sigmoidal models of the neural-cognitive relationship. The sigmoidal model has at minimum three parameters to describe its rate of increase and capacity limitations. It is a multiple parameter model requiring non-linear iterative processes for fitting to data [2].

Melancholic depression is a severe depressive disorder subtype showing a clinical course little influenced by psychological and social factors, in which biological determinants seem to be relevant [4]. Recently, it has been discovered that a general enlargement of brain cerebrospinal fluid (CSF) spaces in patients with severe melancholia, is more prominent in the sylvian fissure region and more evident in the left hemisphere [5]. In this study, a follow-up of the melancholic patients had been investigated to find a possible relationship

between CSF space change and the patient's clinical outcome, using both time to clinical remission and time to eventual symptom relapse or recurrence as outcome measurements.

The presented approach makes use of a differential equation model by re-examining the quadratic model of brain activation with increasing cognitive load. Such a model includes intercept, linear and quadratic components when modeling neural-cognitive relationships. The straight-forward quadratic model is interpreted with respect to the fact that it represents a solution to a first-order differential equation. The application of this polynomial regression is therefore used with differential equation, i.e. a "language of change". Previous descriptions of brain activation increases with a cognitive load may be reframed using a differential equation model.

Methodology

Before moving on with the actual implementation of differential equation models for the prediction of clinical outcomes in melancholia, we need to know what parameters should be considered for the study. These parameters have been also accounted for during the processing of data.

Parameters under study

Patients with melancholic depression are subjected to neuroimaging examinations, particularly Magnetic Resonance Imaging (MRI) which provides a new insight into the biological substratum of depressive illness. Different clinical parameters have been taken into account for the detection of enlarged brain CSF spaces, some of which include:

1. T2 weighted brain images via Fast Spin Echo (FSE).
2. T1 and T2 weighted brain images via fluid-attenuated inversion recovery (FLAIR).
3. Gradient echo T2 weighted transverse images of brain, followed by FSE T2 weighted coronal and sagittal images.
4. FSE T1 weighted sagittal and FLAIR T1 weighted coronal images of brain.

In each case, three-dimensional diffusion weighted images are taken with b-value of 1000 seconds per squared millimetres. CSF volumes are measured for global brain fluid spaces as well as for lateral ventricles and left and right sylvian fissure regions.

Data pre-processing

First, brain images are inspected for the presence of any artifacts preventing further analyses. Pre-processing involves three main steps, i.e. tissue segmentation, normalization and smoothing. In this context, a powerful mathematical tool in order to study the causal relationship between CFS spaces and melancholia, may be the implementation of a differential equation model.

Segmentation

In segmentation, images are segmented in parallel using two different algorithms - the unified segmentation and the new segment [6,7]. In case of parallel segmentation, suppose parameter x represents the intensity of images obtained via FSE, and t represents the cognitive load. Initially, there may be no change in the images produced, with an increase in cognitive load. It may be represented with the differential equation:

$$\frac{dx}{dt} = 0$$

This states that changes in the intensity of T1 images per unit time obtained in Fast Spin Echo, equals zero. Integrating this, we obtain a function of the level of brain activity as:

$$x(t) = c$$

which indicates that measured brain activity, as depicted by the strength of images is at the level *c* for all cognitive loads *t*.

Now, when the intensity of images changes from T1 to T2, the change may be expressed as a constant rate with increase in cognitive loads. So, we have:

$$\frac{dx}{dt} = B$$

Which on integrating gives:

$$x(t) = Bt + c.$$

Therefore, these three-dimensional weighted images are modelled as a linear function of cognitive load with slope *B* and intercept *c* In other words, brain activity, as depicted by images, is at the level when *c* cognitive load is at the lowest level. It changes at a constant velocity *B* as depicted by progression of images from T1 to T2, with increasing levels of cognitive loads.

Now, it is seen that the unified segmentation extracts CSF from raw T images using a probabilistic framework combining tissue classification, image registration and bias correction. On the other hand, the new segmentation uses an extended set of probability maps allowing for a different treatment of images outside the brain (i.e. the ones most likely to be classified as CSF). This algorithm incorporates tissue probability maps of bone and soft tissue [8].

There are several possible forms for determining the tissue segments which build up the probability maps. Some widely used functions include the membrane energy and the bending energy, which in three dimensions exhibit the forms:

$$h = \sum_{i} \sum_{j=1}^{3} \lambda \left(\frac{\partial u(x_i)}{\partial x_{ji}} \right)^2$$

and $h = \sum_i \sum_{j=1}^{3} \sum_{k=1}^{3} \lambda (\frac{\partial^2 u(x_i)}{\partial x_{ji} \partial x_{ki}})^2$ respectively.

Here $\frac{\partial u(x_i)}{\partial x_{ij}}$ is the gradient of the modulating function for the i^{th} image in the j^{th} orthogonal direction and λ is a user-assigned constant. However, for the purpose of modulating the images, a smaller cost function is used that is based on the squares of the third derivatives (third order regularization), which is given by:

$$h = \sum_{i} \sum_{j=1}^{3} \sum_{k=1}^{3} \sum_{l=1}^{3} \lambda (\frac{\partial^3 u(x_i)}{\partial x_{ji} \partial x_{ki} \partial x_{li}})^2$$

This model is chosen because it can produce slowly varying modulation fields that can represent the variety of non-uniformity effects that are likely to be encountered in MRI images [9].

Normalization and smoothing

The rigidly transformed images of CSF spaces derived from both the unified segmentation and the new segment algorithms are normalized. First of all, the diffusion weighted images in both FSE and FLAIR, are iteratively matched to an image generated from its own light and intensity, so as to generate a series of images with increasing resolution [10]. Thus, the rate of modification of the images may itself change as a linear function of cognitive load, giving:

$$\frac{dx}{dt} = 2At + B.$$

Integrating this to obtain a function of intensity of images of the CSF spaces provides:

$$x(t) = At^2 + Bt + c.$$

Then the native space images from brain spaces are registered to the highest resolution CSF image within a high-dimensional diffeomorphic framework (i.e. within a cluster of smooth isomorphic brain images). Spatially normalized tissue maps are then modulated by the Jacobian determinants derived from the corresponding flow-fields to restore the volumetric information lost during the high-dimensional spatial registration.

If *y* and *z* denote the intensity of T1 and T2 weighted images via FLAIR and Gradient echo, respectively, then a three-dimensional Jacobian deformation field can be represented by:

$$J = \begin{bmatrix} \frac{\partial(x-u_x)}{\partial x} & \frac{\partial(y-u_y)}{\partial x} & \frac{\partial(z-u_z)}{\partial x} \\ \frac{\partial(x-u_x)}{\partial y} & \frac{\partial(y-u_y)}{\partial y} & \frac{\partial(z-u_z)}{\partial y} \\ \frac{\partial(x-u_x)}{\partial z} & \frac{\partial(y-u_y)}{\partial z} & \frac{\partial(z-u_z)}{\partial z} \end{bmatrix}$$

Finally, bias corrected, tissue segmented and normalized and modulated CSF images are smoothed with a 5 mm full-width at half maximum (FWHM) isotropic Gaussian kernel [10].

Modelling the arachnoid cystic lesion

Let us consider an infinitesimally small area of brain tissue $\Delta\Omega$ with sides dx and dy. We can present a model considering two classes of arachnoid cystic lesions, growing and migrating, differentiated by their patterns of behaviour (phenotype). Since the lesions are partitioned by phenotype, we include phenotype changes in the conservation equations as well. Here we use only these two characteristics to formulate the two-dimensional conservation equation. Suppose the variables $u(x,t)$ and $v(x,t)$ represent the proliferating glioma cells and the migrating glioma cells respectively. Then we have:

$$\frac{\partial u}{\partial t} = Du(x)\nabla^2 u + \rho u\left(1 - \frac{u+v}{\kappa}\right) - \beta u \ldots \quad (1)$$

$$\frac{\partial u}{\partial n} = u = 0 \; on \; \partial\Omega \ldots \quad (2)$$

$$\frac{\partial v}{\partial t} = Dv(x)\nabla^2 v + \beta v \ldots \quad (3)$$

$$\frac{\partial v}{\partial n} = v = 0 \; on \; \partial\Omega \ldots \quad (4)$$

The first equation describes the dynamics of the variable *u* which gives the number of proliferating cystic lesions throughout the domain. Although the cells are assumed to not actively migrate throughout the brain, an undirected diffusion term is included to represent the random motion. Therefore, the coefficient of diffusion *Du* is very low. However, *Du* varies according to tissue type to account for the fact that some cystic lesions are more permeable than others. Again, it is seen that the cystic lesions reproduce exponentially just like tumour cells, until they reach carrying capacity. So, the first equation also contains a logistic growth term with carrying capacity *k* and growth rate ρ.The term (*-βu)* accounts for the approximate loss of cells due to phenotype change [11]. Also, both *Du* and are *Dv* very small in regions corresponding to cerebrospinal fluid (CSF) reflecting the very small diffusion of cysts in this region.

Numerical solution to clinical outcome in melancholia

The growth of cystic lesions defined above can be solved numerically using finite element analyses to predict the clinical outcome in the treatment of melancholia. For this, we approximate the exact analytical solution with a piecewise linear function.

Variational formulation

In order to solve the system numerically, we first determine the variational formulation of the system of partial differential equations defined in the previous section. For instance, if *u* is a solution to the equation:

$$\frac{\partial u}{\partial t} = Du\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \beta u\right),$$

Then we have:

$$\int_\Omega w \frac{\partial u}{\partial t} d\Omega = Du \int_\Omega (w \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \beta w u)$$

For any function *w* satisfying the same boundary conditions. This formulation allows us to integrate by parts. Given the no-flux condition on the boundary (i.e. outer skull in our case), Green's theorem is implemented to achieve the following form of equations:

$$\int_\Omega w \frac{\partial v}{\partial t} d\Omega = Dv \int_\Omega \left(\frac{\partial w}{\partial x}\frac{\partial v}{\partial x} + \frac{\partial w}{\partial y}\frac{\partial v}{\partial y}\right) d\Omega + \rho \int_\Omega wv\left(1 - \frac{u+v}{\kappa}\right) d\Omega - \beta \int_\Omega wu\, d\Omega$$

$$\int_\Omega w \frac{\partial u}{\partial t} d\Omega = Du \int_\Omega \left(\frac{\partial w}{\partial x}\frac{\partial u}{\partial x} + \frac{\partial w}{\partial y}\frac{\partial u}{\partial y}\right) d\Omega + \beta \int_\Omega wu d\Omega$$

Here, rather than finding the solution *u* or *v* for all functions *w*, it is possible to numerically find a solution *u* with *w* ranging over a finite-dimensional family [12].

Discretization

The solutions *u* and *v*are approximated with functions $\tilde{u}$ and $\tilde{v}$ that are piecewise linear. This requires dividing the domain into a finite number of elements [13]. The elements do not remain equally sized since the domain moves with expansion of the CSF space.

Since cystic lesions are too diffuse and invasive, it is not possible to define an interface between healthy and cystic tissue. Therefore, some traditional methods of continuum mechanics fail since there is not a well-defined boundary where motion occurs. This approach can be problematic, as the elements where CSF enlargement occurs with maximum density, significantly lowers the resolution of the approximate solution [11]. However, here we are considering qualitatively better results, so these problems have not been thoroughly accounted for.

Finite (Linear) approximation

To approximate the exact solution of the model, the solutions *u* and *v* are represented with a finite basis of compactly supported linear functions, which allows the system to be integrated numerically. Since we wish to approximate the solutions $\tilde{u}$ and $\tilde{v}$ to be linear on each triangular element, we choose a basis such that three basis functions are supported on each element, thus representing linear interpolation of the solutions. This means the functions:

$$f_1(x,y) = \frac{1}{2A}[(b_1c_2 - c_1b_2) + (b_2 - c_2)x + (c_1 - b_1)y]$$

$$f_2(x,y) = \frac{1}{2A}[(c_1a_2 - a_1c_2) + (c_2 - a_2)x + (a_1 - c_1)y]$$

$$f_3(x,y) = \frac{1}{2A}[(a_1b_2 - b_1a_2) + (a_2 - b_2)x + (b_1 - a_1)y]$$

are defined on each element where $a= (a_1,a_2)$, $b=(b_1,b_2)$, $c=(c_1,c_2)$ are the three element vertices and A is the element area. These functions satisfy the condition that if d_j is one of the vertices *a,b* or *c* then $f_i(d_j)=\delta_{i,j}$ which is the Kronecker Delta Function [11]. Further, $\sum_{i=1}^{3} f_i = 1$ as desired. Therefore, on each element *e*.we make use of the approximate linear solutions

$$\tilde{u}_e = \sum_{i=1}^{3} f_i(x,y)u_i \quad \text{and}$$

$$\tilde{v}_e = \sum_{j=1}^{3} f_j(x,y)v_j$$

where $u_i$and $v_j$are the values of *u* and *v* at nodes *i* and *j* respectively. Generalizing to the entire domain, we use the global approximations

$$\tilde{u} = \sum_{e=1}^{n}\sum_{i=1}^{3} f_{e,i}(x,y)u_{e,i} \quad \text{and}$$

$$\tilde{v} = \sum_{e=1}^{n}\sum_{j=1}^{3} f_{e,j}(x,y)v_{e,j}$$

where $f_{e,i}$ is the function f_i local to the element *e*, $u_{e,i}$ is the value of *u* at node *i* on element *e* and *n* is the total number of elements.

Now, let the function *w* range over a finite-dimensional family of functions defined on the domain, i.e. we use

$$w = \sum_{e=1}^{n}\begin{bmatrix} f_{e,1}(x,y) \\ f_{e,2}(x,y) \\ f_{e,3}(x,y) \end{bmatrix}.$$

Integrating in both spatial dimensions then gives us the following linear system of ordinary differential equations [14]:

$$[M][\dot{v}]^t = [K_v][v]^t - \rho[M]\left[v\left(1 - \frac{v+u}{\kappa}\right)\right]^t - \beta[M][u]^t$$

$$[M][\dot{u}]^t = [K_u][u]^t + \beta[M][u]^t$$

Discussion

In this article, we employed the use of ordinary differential equations to model the dynamics of cystic lesions causing an increase in the area of cerebrospinal fluid spaces. Also, modeling has been used for a possible treatment of the lesions, which can do away with melancholia. The limitation, however, is that the model has been implemented with an initial approximation in the behaviour of cysts, which can eventually lead to tumour.

Perhaps the most important area for development is to model the mass-effect that occurs due to brain surgery. First of all, since the effects of gravity are not considered in the current model discussed, a method needs to be developed for modeling the collapse of the resection cavity post-surgery. Inaccuracy due to a simplified, linear model of cellular deformation can be ignored, atleast in early cystic lesions, because the extent of the mass-effect is relatively small. However, after the resection of even a small cyst, the patient's brain undergoes a dramatic deformation in a short span with collapse of the resection cavity. Therefore, a linear model of brain CSF spaces is unlikely to provide an accurate method of modeling such an event [15].

The models here demonstrate for the first time the neurobiological pathways that predict syndromal depression and melancholia, consistent with a multidimensional model of the same [16]. The specific pathway to syndromal melancholia in this article, is based on previous integrative findings and with behavioural formulations that distinguish a depression factor defined by anhedonia and lack of positive emotion [17].

However, a crucial factor to be noted is that arachnoid cysts are usually asymptomatic. Symptoms from an arachnoid cyst are caused by an increase in the osmotic gradient of the liquid content of the cyst, the creation of a valve mechanism between the arachnoid cyst and the subarachnoid space leading to an increase in the size of the cyst, or the secretion of liquid from the cyst wall thus enlarging the cyst. The onsets of symptoms are in most of the cases, due to the obstruction of CSF circulation [18]. The differential diagnosis of an arachnoid cyst of the cerebellopontine angle includes other cystic lesions (epidermoid and neurenteric cyst, cystic acoustic schwannoma). MRI is helpful in differentiating arachnoid cysts from those cystic lesions. On MRI, arachnoid cysts appear to be a smooth surface that possesses a signal characteristic of CSF. In contrast, epidermoid cysts show mixed signals on FLAIR images and high signals on diffusion weighted images. Neurenteric cysts present high responses to T1-weighted images and cystic schwannomas show some foci of contrast enhancement on T1-weighetd post-contrast images [19,20].

Conclusion

The MR image–generated CSF volumes are considerably larger than the combined cranial and spinal CSF volumes determined from ventriculolumbar perfusion studies of patients with normal or slightly enlarged ventricles [21]. The volume occupied by arachnoid trabecular and small blood vessels normally found within the cranial subarachnoid space is not discriminated from CSF by MR image segmentation. Consequently, this volume is included in the extraventricular CSF volume determination. The age-dependent expansion of the extraventricular CSF volume could therefore be due to an increase of the cranial subarachnoid space and the extraventricular CSF space. Till now no study has been found in which the volume occupied by these structures has been determined or whether this volume changes with age. If such structures do occupy a significant fraction of this space, the disparity between the MR image and more traditionally generated values may be explained.

However, if they do not, MR imaging segmentation may be identifying an extraventricular CSF compartment that heretofore was unrecognized. Computerized MR image processing segmentation provides a non-invasive *in vivo* technique to measure intracranial, brain, and ventricular and extraventricular CSF volumes that avoids many of the aspects associated with traditional methods. This technique can be expected to improve our knowledge of physiological and biochemical processes that affect these cranial compartments throughout life. In addition, it should provide a powerful tool to better understand and manage clinical problems associated with the various types of ventricular enlargement [22].

The treatment model discussed in this article is only based on a single treatment measure. It may be more effective for the treatment of melancholia if we add a medication during the recovery stage, which are still an open problem and a scope for future research work.

Bibliography

1. Steffener J., *et al*. "Quantifying Neural Efficiency and Capacity: A Differential Equation Interpretation of Polynomial Contrasts". *arXiv* (2016): 1606.06249.
2. Jackson T., *et al*. "Mathematical oncology: using mathematics to enable cancer discoveries". *The American Mathematical Monthly* 121.9 (2014): 840-856.
3. Gatt JM., *et al*. "Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety". *Molecular Psychiatry* 14.7 (2009): 681-695.
4. Zimmerman M., *et al*. "The validity of four definitions of endogenous depression: II. Clinical, demographic, familial, and psychosocial correlates". *Archives of General Psychiatry* 43.3 (1986): 234-244.
5. Pujol J., *et al*. "CSF spaces of the Sylvian fissure region in severe melancholic depression". *Neuroimage* 15.1 (2002): 103-106.
6. Ashburner J and Friston KJ. "Unified segmentation". *Neuroimage* 26.3 (2005): 839-851.
7. Ashburner J., *et al*. "Functional imaging laboratory: wellcome trust centre for neuroimaging". SPM8 Manual. London, UK (2011).
8. Via E., *et al*. "Cerebrospinal fluid space alterations in melancholic depression". *PloS one* 7.6 (2012): e38299.
9. Ashburner J and Friston KJ. "Image Segmentation". The Wellcome Department of Imaging Neuroscience (2011).
10. Ashburner J. "A fast diffeomorphic image registration algorithm". *Neuroimage* 38.1 (2007): 95-113.
11. Hines T. "Mathematically modeling the mass-effect of invasive brain tumors". Arizona State University (2010).
12. Amberger-Murphy V. "Glioma invasion: mechanism, modulation and future possibilities". *Acta Neurochirurgica* 145.8 (2003): 613-614.
13. Anderson E., *et al*. "Angiogenesis in Glioblastomas Multiforme: LAPACK User's Guide -3rd Edition". Society for Industrial and Applied Mathematics (1999).
14. Cocosco CA., *et al*. "Brainweb: Online interface to a 3D MRI simulated brain database". In NeuroImage (1997).
15. Miller K and Chinzei K. "Mechanical properties of brain tissue in tension". *Journal of Biomechanics* 35.4 (2002): 483-490.
16. Clark LA and Watson D. "Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications". *Journal of Abnormal Psychology* 100.3 (1991): 316-336.
17. Kemp AH., *et al*. "Predicting severity of non-clinical depression: Preliminary findings using an integrated approach". *Journal of Integrative Neuroscience* 5.1 (2006): 89-110.
18. Eslick GD., *et al*. "Diplopia and headaches associated with cerebellopontine angle arachnoid cyst". *ANZ Journal of Surgery* 72.12 (2002): 915-917.
19. Brackmann DE., *et al*. "Extra-axial neoplasms of the posterior fossa". *Otolaryngology Head and Neck Surgery* 4 (1998): 3294-3330.

20. Bonneville F., *et al*. "Unusual lesions of the cerebellopontine angle: a segmental approach". *Radiographics* 21.2 (2001): 419-438.

21. Lorenzo AV., *et al*. "Cerebrospinal fluid absorption deficit in normal pressure hydrocephalus". *Archives of Neurology* 30.5 (1974): 387-393.

22. Matsumae M., *et al*. "Age-related changes in intracranial compartment volumes in normal adults assessed by magnetic resonance imaging". *Journal of Neurosurgery* 84.6 (1996): 982-991.

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