Research Article

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Model analogies between pattern formation in deforming engineering materials & morphogenesis in ageing human brains

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Abstract: Mathematical models developed within the material mechanics and material physics communities have been routinely adapted to interpret and further understand physiological and biological processes. The field of biomechanics, in particular, has emerged from a direct application of elasticity and fluid mechanics theories to model cell and tissue behavior, as well as bone fracture and blood flow. On the other hand, Turing's reaction-diffusion model of morphogenesis for biochemical systems has been adapted to interpret pattern formation in deforming materials. An important aspect, however, that has not been sufficiently examined is to investigate the role of an externally applied or internally developed stress. Another, equally interesting issue that has not been adequately explored, concerns the development of a common effective methodology to analyze signals and images for both humanmade and naturemade systems, especially when differential equations are not available to use for this purpose. The article is an initial modest effort to discuss such common features between nonliving and living materials. It focuses, in particular, to modeling analogies between pattern formation of defects in deforming engineering materials under application of external stress and morphogenesis of cellular structures in ageing brain tissue under development of internal stress.

Keywords: pattern formation/morphogenesis, nanomaterials/brain, Alzheimer

1 Introduction

The recent advances in continuum and statistical mechanics, as well as the recent developments in novel experimental probes and nanodevices, have enabled modeling and observations to proceed hand-in-hand at the same time and space scales. In particular, the emergence of new fields of nanoscience and nanotechnology has led to the formulation of new models as well as theoretical, experimental and numerical methodologies that can be used to both nanomechanics/nanoengineering and nanobiology/nanomedicine applications.

A new continuum mechanics framework that has been formulated for modeling material behavior across the scale spectrum is Aifantis gradient theory for deformation and diffusion processes in the presence of evolving micro/nano structures [1–5]. It is based on the introduction of extra Laplacian terms in the classical constitutive equations (e.g. Hooke's and Fick's laws) to incorporate nonlocality and deterministic scale effects. Stochasticity can be introduced through additional non-deterministic terms to model the effect of randomly evolving micro/nano structures [6]. When differential equations are not available or cannot be derived to interpret the system's response, statistical analyses should be employed for material/process characterization. A rather new statistical mechanics tool, that can effectively be used for signal/image analysis throughout the observation spectrum, is Tsallis q -statistics based on nonextensive entropy thermodynamics [7–10].

A recent review elaborating on the above ideas, by also extending them to include fractional/fractal considerations, is provided in [11]. Defect patterning models are not included in this review which, thus, needs to be supplemented by referring to the original articles for the periodic ladder-like structure of persistent slip bands during cyclic deformation (the W-A model [12]), as well as to the periodic spatial structure of misorientation bands during monotonic deformation (the R-A model [13]). In view

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Figure 1: (i) Persistent slip band (PSB) and dislocation multipole matrix (M) formation in fatigued Cu crystals; (ii) The corresponding system of R-D type equations for immobile and mobile dislocations (W-A model); (iii) Solutions of the W-A equations describing the periodic structure of PSBs; (iv) The evolution of stress (τ) – strain (γ) curve showing the constancy of stress during PSB formation. For related details the reader can consult [1, 3, 11b] and references quoted therein.

of this, we present in Section 2 the basics of gradient theory as applied to pattern formation under external stress and the resulting self-organization of structural defects (dislocations, disclinations) in crystals and nanomaterials. We focus, in particular, on the Walgraef-Aifantis (W-A) model for single crystals under cyclic applied stress [12] and the Romanov-Aifantis (R-A) model for single crystals under monotonic applied stress [13]. We then we summarize the governing equations for the evolution of structural defects in nanopolycrystals. In Section 3, and in analogy to the evolution equations for structural defects in nanomaterials, differential equations for the interaction of various families of cells in the human brain during neurodegeneration are proposed. In Section 4, a summary of Tsallis q -statistics is provided and applications to signal/image analyses for both metal deformation and brain deterioration are given. Some relevant results on a preliminary anal-

ysis of electroencephalograms (EEG) are summarized in the Appendix. Finally, in Section 5, some closing remarks for this initial effort on modeling analogies between nonliving and living systems are given, along with some related remarks for future directions.

2 Pattern formation of material defects during deformation

In Figure 1, the W-A model for dislocation patterning in single crystals under cyclic deformation is illustrated. The remarkable phenomenon of persistent slip band (PSB) formation with wave length λ_c is shown. The quantities (ρ_i , ρ_m) designate the density of immobile/mobile dislocations; (D_i , D_m) are the corresponding gradient (diffusion-

Disclination-dislocation kinetics and patterning

$$\frac{\partial \rho}{\partial t} = F(\rho) - L(\vartheta)B\rho^2 - M\rho\vartheta + D\frac{\partial^2 \rho}{\partial x^2}; \quad \frac{\partial \vartheta}{\partial t} = -Q(\vartheta) + \mu M\rho\vartheta$$

ρ - density of mobile dislocations;

ϑ - density of immobile disclinations

The solution for reaction-kinetic equations

[A.E.Romanov, E.C.Aifantis, Scripta Met. Mat. 29 (1993) 707]

EBSD orientation map image Al, 40% cold rolling

Figure 2: The R-A model for dislocation (ρ)– disclination (θ) populations, its spatially periodic solution and its applicability to interpret periodic orientation bands observed in electron micrographs. For related details the reader can consult [3, 11c] and references quoted therein.

like) coefficients depending on the applied stress; whereas the quantities $g(\rho_i)$ and $h(\rho_i, \rho_m)$ denote the corresponding production and creation/annihilation terms. In particular, the term $h(\rho_i, \rho_m) = \beta\rho_i - \gamma\rho_m\rho_i^2$ designates the creation of mobile dislocations at the expense of immobile ones with rate β , and their immobilization by immobile dipoles at rate γ . Both of these rate coefficients depend on the applied stress. Since the applied cyclic stress remains constant during PSB formation, all the above phenomenological coefficients may be taken as constants. The simple one-dimensional reaction-diffusion type model (the W-A model) was the first one proposed to interpret on a purely phenomenological basis the experimentally observed transmission electron microscope (TEM) images.

An extension of the aforementioned W-A model may be established by considering, in addition, an extra set of equations for the mechanical stress σ /strain ε fields of the form $\dot{\varepsilon} - D_\varepsilon \partial_{xx} \varepsilon = k\sigma^n$; $\partial_{xx} \sigma = \ddot{\varepsilon}$, where (D_ε, k, n) are new phenomenological constants; (k, n) are the standard material constants of viscoplasticity and D_ε is a new gradient coefficient for the local strain ε . The first equation is a gradient generalization of the standard viscoplastic constitutive equation for homogeneous deformations, and the second equation is the time derivative of the stan-

dard dynamic equilibrium equation in one dimension. For quasi-static deformation ($\ddot{\varepsilon} = 0$), and on the assumption that the W-A constants depend on the macroscopic strain, the study is significantly simplified. Another simpler alternative is to assume that the kinetic coefficients in the W-A model depend on the local stress τ related to the global stress σ through the gradient expression $\tau - D_\tau \nabla^2 \tau = \sigma_0$, or the diffusion-like equation $\dot{\tau} - D_\tau \nabla^2 \tau = \sigma_0$. These are intuitive generalizations, the implication of which on stability and pattern formation needs to be examined.

In Figure 2 an analogous reaction-diffusion type model (the R-A model) was proposed for dislocation (ρ) – disclination (θ) kinetics, leading to a spatially periodic pattern for the resulting misorientation bands.

In Figure 3, an extension of the W-A and R-A models is proposed for the defect kinetics in deforming nanopoly-crystals: ρ is the density of intragrain “fast” moving dislocations; φ is the density of the corresponding slow moving dislocation dipoles; ψ is the density of mobile grain boundary dislocations; and θ is the density of slow moving disclinations at triple grain boundary junctions. The linear parameter d denotes grain size and the angular parameter ω denotes the strength of disclinations. The gradient coefficients D 's ($D_\theta < D_\varphi \ll D_\rho \simeq D_\psi$) characterize the de-

NanoDefect Kinetics [Selforganization at the Nanoscale]

• Nanopolycrystals

$$\rho_t = A_\rho \rho - B_\rho \rho^2 - C_0 \frac{\rho}{d} + C_3 \rho \varphi + \omega M \vartheta + N \frac{\psi}{d} + D_\rho \nabla^2 \rho$$

$$\varphi_t = A_\varphi \rho + B_\varphi \rho^2 - C_4 \rho \varphi - K \varphi + D_\varphi \nabla^2 \varphi$$

$$\psi_t = C_1 \frac{\rho}{d} + A_\psi \psi - B_\psi \psi^2 + D_\psi \nabla^2 \psi$$

$$\vartheta_t = C_2 \frac{\rho}{\omega d^2} - P_1 \rho \vartheta - P_2 \psi \vartheta - G \vartheta + D_\vartheta \nabla^2 \vartheta$$

ρ – mobile dislocations in the grain interior

φ – low-mobility (immobile) dislocations (dipoles)

ψ – grain boundary sliding dislocations

ϑ – immobile junction disclinations

Figure 3: Reaction-Diffusion (R-D) type equations for the dominant families of structural defects in nanopolycrystals.

fect kinetics, while the remaining phenomenological coefficients characterize the defect reactions. Under the assumption $D_\theta \simeq D_\varphi \simeq 0$ and on adiabatic elimination of φ with respect to ρ , the reduced simpler system of three differential equations can be much easier analyzed. Under further assumptions, a formal reduction to the W-A and R-A models is also possible for describing the evolution of cell populations during neurodegeneration, as discussed below.

3 Self-organization of brain cells during neurodegeneration

Dementia (MCI/ Mild Cognitive Impairment) is one of the most frequently diagnosed brain disorders (reported episode frequency 0.33/sec world-wide), with Alzheimer disease (AD) being its most common form (lethal, expensive and societal burden) in the 21st century. In Figure 4, a simplified pictorial illustration of mutual interaction of the dominant families of brain cell/constituents during AD progression is given. A corresponding previously proposed mathematical kinetic model [14] for such brain entity populations (active and nonactive microglia; quies-

cent and proliferating astroglia, surviving and dead neurons, as well as A β amyloid) is summarized in Figure 5. It is noted that the spatial evolution of cells is not accounted for, and diffusion terms are neglected. Motivated by this model, it is suggested here to consider reaction-diffusion (R-D) type equations for two families of brain cells (microglia/astroglia combined and neurons), along with an extra equation for the growth of A β senile plaques. Then, the resulting system of differential equations will involve two R-D equations for microglia-astrocytes (M) and amyloid beta protein (A β), along with two rate equations for neurons (N) and senile plaques (Sp) which respectively decrease and increase during AD progress. The effect of internal mechanical stress developed as a result of cell-extracellular matrix (ECM) interactions can be taken into account in a manner similar to that earlier done for the W-A model.

4 No equations & Tsallis q-statistics

Standard deterministic gradient models cannot provide any information on measured statistical aspects of plas-

Cell Interaction Processes During AD Progression

Figure 4: Pictorial representation of cell processes during Alzheimer disease (AD).

tic deformation, such as fractal dimensions for deformation patterns; power-law exponents for dislocation avalanches [15, 16]; and strain bursts recorded during nanoindentation [17] or micro/nanopillar compression tests [18–20]. When differential equations cannot be invented to interpret experimental data and simulations, system characterization is left to statistical analyses for obtaining fractal dimensions and establishing universal power-laws. In many cases, however, the usual power-laws based on Boltzmann-Gibbs statistics exclude the regime of low intensity-high probability events. Tsallis q-statistics [21–23] based on nonextensive entropy thermody-

namics remove this difficulty and can be employed here to analyze intermittent plasticity and deformation patterned images obtained experimentally. This information also allows for the construction of appropriate PDFs to be used in the aforementioned combined gradient-stochastic models. Tsallis nonextensive (non-additive) q-entropy reads $S_q = k(1 - \sum_i p_i^q)/(q-1)$ and by letting $q \rightarrow 1$, the familiar Boltzmann-Gibbs extensive entropy is recovered. Corresponding q-distribution functions (q-Gaussian, q-exponential, q-Weibull) are obtained, which for $q \rightarrow 1$ reduce to their standard counterparts.

A Mathematical Kinetic Model for AD

Species Populations: Microglia (M); Astroglia (A); Neurons (N) and Amyloid- β ($A\beta$)

Schematic of the AD mechanism that incorporates feedback influences from surviving and dead neurons N_s and N_d , quiescent and proliferating astroglia A_q and A_p , reactive and normal microglia, M_1 and M_2 and $A\beta$.

$$\begin{aligned} \frac{dN_s}{dt} &= \alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1; & \frac{dN_d}{dt} &= -\frac{dN_s}{dt} \\ \frac{dA_q}{dt} &= \alpha_4 M_2 - \alpha_5 M_1; & \frac{dA_p}{dt} &= -\frac{dA_q}{dt} \\ \frac{dM_2}{dt} &= (\alpha_6 + \alpha_{11}) N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12}) A_q - \alpha_9 M_1 + \alpha_{14} M_2 - (\alpha_8 + \alpha_{13}) A\beta \\ \frac{dM_1}{dt} &= -\frac{dM_2}{dt}; & \frac{dA\beta}{dt} &= \alpha_{15} N_s - \alpha_{16} M_2 \end{aligned}$$

Figure 5: Mathematical model consisting of 7 kinetic equations for brain cell populations and $A\beta$ amyloid protein. For related details of model development and numerical solutions the reader can consult [14].

Serrated Plastic Flow & Multiple Shear Banding in UFGs

(Fan et al. Scripta/Acta Materialia 2005/2006)

Figure 6: Serrated stress-strain curves, corresponding to electron micrograph images of shear band formation and respective time series analyses. For related details the reader can consult [7] and references quoted therein.

Serrations: q-PDFs/no Power Laws

•Tsallis q - Gaussian: $P(s) = p_0[1 + (q-1)\beta_q(s)^2]^{1/(1-q)}$

•Fitting: $\ln_q(P(s_i))$ vs s_i^2

•Power Law Tail ($q > 1$): $P(|s|) \sim |s|^{-2/(q-1)}$

$q > 1 \rightarrow$ { Non-Gaussian Statistics
Tsallis Nonextensive Statistics,
Temporal Long range correlations

Shear Banding: Fractality

$D > 2 \rightarrow$ Fractal Geometry of Shear Band network

$q > 1 \rightarrow$ { Non-Gaussian Pixels Distributions
Spatial Long range correlations

Figure 7: Tsallis q -statistics analysis for power-like laws and fractality of the experimental data presented in Figure 6. For related details the reader can consult [7] and references quoted therein.

Figure 8: Initial preliminary results: (a) Fractal dimension (FD) analysis of MRI tomography provides 80% accuracy in diagnosing AD disease: healthy brains (FD=3.51); AD brains (FD=3.3). These are very suggestive results from an extremely limited pool of data indicating that 9/11 AD brains are characterized by FD between 3.14 and 3.32, whereas 4/5 healthy brains are characterized by FD between 3.32 and 3.38. [Courtesy of M. Tsolaki Medical School of Aristotle University and I.N. Nikolaidis]

EEG Epileptic Regime

Figure 9: **a)** Time series of epileptic episode. **b)** Filtered EEG time series corresponding to **a)**. **c)** Best linear correlation between $\ln_q[p(\varepsilon_i)]$ and ε_i^2 for the filtered signal. **d)** $\log[p(\varepsilon_i)]$ vs ε_i for the filtered EEG time series (blue circles), the theoretical q-Gaussian (blue line) and the normal Gaussian (green line).

Figure 10: Microscopy images showing the structure of senile Aβ plaques. **a)** Brain tissue observed in the electron microscope after 3 years preservation in paraffin. **b)** Biopsy material [Courtesy of S. Baloyiannis, Neurology Department of Aristotle University]

In Figures 6 and 7, the application of Tsallis q-statistics in analyzing signal (stress/strain curves)/image (electron microscopy) observations in ultrafine grain (UFG) polycrystals is shown, and the departure from standard Boltzmann-Gibbs statistics is illustrated. In Figure 8, related magnetic resonance imaging (MRI)/preliminary analyses from healthy and AD brains are presented, while in Figure 9, corresponding Tsallis q-statistics results are summarized, as obtained from electroencephalograms (EEG) of patients with epilepsy. Finally, in Figure 10, typical electron microscopy image of senile plaques observed in AD patients is shown. It is hoped that fractal and lacunarity dimensions obtained through these images may differentiate between healthy and AD brains.

5 Conclusions

A discussion has been provided on qualitative and quantitative analogies between models and methodologies used for understanding the spatio-temporal evolution and self-organization of structural defects in novel engineering materials on one hand, and the pattern formation and morphogenesis in brain cells and tissue on the other. Evolution equations for various families of structural defects in deforming nanomaterials are shown to resemble corresponding differential equations for various families of cells/proteins in ageing brains. Even though the discussion is purely phenomenological, the stage has been set up for supplementing it with mechanism-based arguments and related numerical simulations. When the experimentally recorded data for signals and images cannot be interpreted through deterministic models and corresponding differential equations are not available to analyze, the methodology of Tsallis q -statistics seems to be promising for capturing statistical features of the observed behavior for both nonliving and living systems. It is hoped that such type of approaches may elucidate the underlying mechanisms for both material and brain damage leading to restoration/repair procedures to be used in both advanced engineering and medical technologies.

In view of the rapid progress in both new design of nanoscopic experimental probes and more efficient computational methods (big data analyses, machine learning methods), it seems that corresponding transfer of knowledge in material/process modeling across scales and disciplines has not been sufficiently attended. The examples briefly considered in the paper suggest the need for more interdisciplinary work along these lines. A more persuasive and detailed discussion is provided in [11a].

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Figure A1: Indicative whole EEG Probability Density Functions for Healthy (Normal), MCI and AD samples.

Appendix: EEG Analysis using Tsallis Entropy (TE) & Higuchi Fractal Dimension (HFD)

Within the context of the analysis explained in the main body of this manuscript, EEG samples were collected from a 10-20 electrode system placement, over 100 subjects (30 healthy, 16 probable AD, and 54 MCI) from an EEG setup with 21 electrodes, and in particular a NIHON KOHDEN Neurofax JE-921A, digitized and analysed with Neurofax EEG-1200. Based on the available signals, the study aimed to explore the potential of diagnosing and differentiating AD, starting from the initial stages of MCI. All of the subjects were examined and diagnosed by experts at the Greek Association of AD and Related Disorders. A battery of neuropsychometric tests has also been provided to evaluate future findings better. The EEG signals were collected following the 10-20 placement system (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, A1, A2) at 500Hz. The input impedance was set to $Z < 10k\Omega$. The protocol employed for the acquisition of the EEG signals refers to resting stage and lasts for 10 minutes with 5 minutes eyes closed and 5 minutes eyes open. A one minute

window was used during eyes closed for the analysis of the EEG signals. Low and high band pass filters have been applied to remove any artifacts prior to analysis, including a filter on 50Hz for noise from electrical equipment, whereas specific zone band filters were applied to retrieve the different EEG rhythms.

For calculating Tsallis entropy, the probability density function (pdf) was found and normalized for every examined signal. Initial findings of a first uniform sample from all three groups/classes (Healthy/Normal, MCI and probable AD) indicate significant changes between Healthy vs. (probable) AD, and MCI vs. AD, but only mild ones between Healthy vs. MCI, even from the fundamental comparison of the pdf, as can be observed in Figure A1.

By calculating the TE and HFD for each electrode and the different basic bands for all three classes, we have so far identified that it is extremely difficult for TE and HFD (with the configuration parameters explored) individually to provide valuable insight for the differentiation between Normal/Healthy, MCI and AD subjects. Nevertheless, certain characteristics are in line with the literature, but more elaborate research is required. In Figure A2, a typical experimental result is given for Tsallis entropy and in Figure A3, another typical result is given for the Higuchi fractal di-

Figure A2: Average Normalised Tsallis Entropy (TE) per electrode and band for the three sample groups (1' examined interval – closed eyes).

Figure A3: Average Higuchi Fractal Dimension (HFD) per electrode and band for the three sample groups (1' examined interval – closed eyes).

Figure A4: Addition of TE and HFD per electrode and band for the three sample groups (1' examined interval – closed eyes).

mension. More details can be found in [10] and references quoted therein.

The combination of TE and HFD to identify a new metric has also been initiated with a simple addition providing some improvements as can be seen in Figure A4. In ongoing work, a larger sample pool is examined along with more combination methods such as Support Vector Machines. It is interesting to note that certain characteristics can be isolated from such analysis for specific bands (*i.e.* delta band). It would appear that the TE offers more distinct deviations than the HFD, however their combination could offer added value to extract specific thresholds, as well as biomarkers for using EEG as a diagnosis method for MCI and AD.