CURRICULUM VITAE

NAME:	**Andreas Hadjiprocopis**
NATIONALITY:	**Cypriot** / **British** & **EU** passports
EMAIL:	`andreashad2@gmail.com`

EDUCATION :

- 1994 – 2000 : School of Informatics, City University, London. Ph.D. Computer Science / Artificial Intelligence, thesis title : "*Feed Forward Neural Network Entities*". Supervisor: Dr Peter Smith.

- 1990 – 1993 : B.Eng. First Class Honours Degree in Electrical, Electronic & Control Engineering[1]. School of Engineering, City University, London.

EXPERIENCE :

- 2015 – today : **Freelance Software Consultant**

  ▶ Leading various computing projects in Cyprus relating to data harvesting and intelligent analysis.

- 4/2013 – 11/2014: **Experienced Researcher, 4D-CH-WORLD, Marie Curie, IAPP (funded by ERA/FP7), Cyprus University of Technology**.

  ▶ **Development of a software pipeline for the 3D reconstruction of structures, objects, faces exclusively from 2D photographs**. The workflow was used to large structures such as cultural heritage monuments but can easily be used for any object given a number of photographs covering its surface. Photogrammetry is an active field of research which is now very relevant because of the increasingly cheap processing power we have at our hands. It is a cheap alternative to laser scanning yielding similar accuracy.

- 10/2009 – 2/2013: **Higher Scientific Officer, Institute of Cancer Research, London**. Research projects (see also `http://nfkb.scienceontheweb.net/`) :

  ▶ **Large-scale integration and intelligent analysis of big data** : design and implement / program machine learning algorithms to deal with the complexities of big (and noisy) data in order to extract Information and Knowledge. To this end I use cluster computers regularly and various computer languages, perl and R for prototyping an idea and mostly C, C++, Java for production. Parallelism of workflows is imperative.

  ▶ **Analysis of single cell images from the Opera automated, high-throughput microscope**: using Machine Learning techniques to correlate cell line, cell morphology, NF-κB expression in nucleus and cytoplasm, cell invasiveness under different conditions (e.g. Hypoxia) or treatments (e.g. TGFα). Integration with data from targeted knockdowns and gene expression arrays for correlating genotype with phenotype.

  Investigation of ergodicity and intracellular noise in the ensemble. Modelling using random boolean networks and sampling the attractors using Monte Carlo methods (with Dr Chris Bakal and Dr Julia Sero, ICR).

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[1] And also first in class of 1993.

- ► I have **integrated Mass Spectrometry data** (SILAC enrichment, phosphorylation) with on-line, **public databases** (e.g. STRING, GO) in order to build **protein-protein interaction networks**. This procedure was used in the investigation of protein expression fold change in cells under Hypoxia and Normoxia conditions.

  I have also developed a novel way of identifying proteins acting as probable connections between protein interaction networks, which the MS failed to detect (with Prof Chris Marshal, ICR).

- ► I have developed methods for analysing **MALDI** (Matrix-assisted laser desorption / ionization) images within a machine learning framework – identification of tissue type, tumour, treatment condition. Fusion with microscope images (with Dr Janine Erler, ICR).

- ► I have developed a **Feature Selection workflow** using a novel algorithm combining **Support Vector Machines** and **Genetic Algorithms**. The workflow is written in C and Java and is especially suited for **SGI's Altix UV supercomputer** system and its shared memory features.

- ► I have rewritten code for Feed Forward Neural Networks and Support Vector Machine to run efficiently on SGI's Altix UV supercomputer and take advantage of its huge shared memory.

- 2005 – 2008 : **Lecturer in the Computer Studies Department, Higher Technical Institute, Nicosia, Cyprus**.

Taught subjects (including setting and marking exams and coursework) :

- ∗ Artificial Intelligence
- ∗ Computer Graphics with OpenGL
- ∗ Game Programming using AI in Java
- ∗ Introduction to C/C++
- ∗ Java Programming
- ∗ Data Communications
- ∗ Online Systems

In addition, I was responsible for supervising students' final year projects such as : **Evolving Virtual Creatures**, **Intelligent Traffic Light System**, **Computer Backgammon Engine**, **e-Voting**, **Mobile Phone Game Programming**, **Evolving a race driver using Genetic Algorithms** (won the HTI's "best computer science project" prize for 2006-07).

- july, 2005 : **Visiting Researcher** at the **Cyprus Institute of Neurology and Genetics** and the **University of Cyprus** in a project entitled "*Brain Segmentation and Morphological Analysis of Magnetic Resonance Images of patients with Multiple Sclerosis*" in collaboration with Prof C.Pattichis (University of Cyprus) and Dr M.Pantzaris (Neurologist, Institute of Neurology and Genetics).

- 2001 – 2004 : **Research Scientist** at the **Institute of Neurology, University College London**, department of Neuroinflammation (Head of Department: Prof D.H.Miller, Director: Prof A.Thompson)

My research was funded by Multiple Sclerosis Society UK and was in the area of analysis of brain Magnetic Resonance Images (MRI, fMRI, DTI) using Machine Learning:

Image segmentation of the brain (white & gray matter and cerebrospinal fluid) using various optimisation methods such as Simulated Annealing, Markov Chain Monte Carlo for entropy minimisation.

Segmentation of Multiple Sclerosis lesions using mixtures of Neural Network experts and clustering.

Quantitative Analysis of lesions using functional MRI (fMRI) and Diffusion Tensor Imaging, DTI.

Implementation of algorithms in C/C++ in a UNIX environment.

• 2000 – 2002 : **Visiting Scholar** at the **Department of Economics, City University, London**, in collaboration with Prof D.Glycopantis.

• 2000 – 2001 : Deckchair.com (London), **Senior Java Developer**. Development of methods and algorithms for the analysis and safe prediction of supply and demand of airplane seats in the travel industry. The methodology was based on my PhD research on how to analyse very large datasets using neural networks.

• 1994 – 2000 : **City University (London)**. Delivered various tutorials to the students of the School of Informatics of City University. Subjects included ARTIFICIAL INTELLIGENCE, DISTRIBUTED SYSTEMS, OBJECT ORIENTED PROGRAMMING, etc.

• 1994 – 2000 : For the needs of my PhD, I have designed and implemented a language (*np*), its compiler and a visual programming environment for creating and training neural network entities. The most prominent feature of *np* is its ability to parallelise the training process of an entity and assign each task to different workstations over a network using TCP/IP.

• 1994 – 1995 : Dr Gus Alusi and **the Ear, Nose and Throat Hospital, London**. Development of methods and algorithms for the triangulation of 3D MRI brain scans, part of a project for "**Virtual Reality Assisted Surgery**".

REVIEWS :

• 2008 – 2011: Invited expert evaluator and rapporteur for the FP7 Marie Curie Actions "Initial Training Networks (ITN)" proposals (FP7-People-ITN-2008 to 2011), Mathematics and Engineering Panel.

• 2004 – : Reviewer for **IEEE**'s *Transactions on Neural Networks*. (Associate Editor : Prof N.B.Karayiannis, `Karayiannis@UH.EDU`).

COMPUTER PROGRAMMING :

• 25 years experience in C • 18 years experience in JAVA • 20 years experience in PERL • 14 years experience in C++ • 5 years experience in R at a very advanced level • 25 years experience in LaTeX • excellent programming & scripting skills under all flavours of UNIX environment • scripting in BASH, CSH, SH probably for ever • parallel-C and OCCAM for parallel processing in a transputer system • I have taught C/C++ & JAVA at university graduate level • some experience in GPGPU programming using CUDA • I am an avid proponent of free software. All my programs are public domain, distributed under GP License.

NATURAL LANGUAGES :

• Near perfect command of Greek • Excellent command of English • Less than average command of French • Fragments of Chinese and Japanese.

INTERESTS :

- Artificial Intelligence • Dynamical Systems, Computation at the Edge of Chaos • Solution of optimization problems using Neural Networks and Parallel Computing environments • Deep Learning • Computational Systems Biology • Image and Signal Processing focusing on Medical Image Processing • Simulated Annealing, Markov Chain Monte Carlo • Cellular Automata • Evolutionary Computer Graphics • Simulation of plants and plant ecosystems • GPGPU

WEBSITES & REPOSITORIES :

▸ Data analysis website at `http://nfkb.scienceontheweb.net/`

▸ Public software repository (Git) at `http://github.com/hadjiprocopis`

▸ Google Scholar profile at `http://scholar.google.com/citations?user=buj_JX4AAAAJ`

LIST OF PUBLICATIONS

NAME: **Andreas Hadjiprocopis**

NATIONALITY: **Cypriot** / **British** & **EU** passports

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BOOK CHAPTERS

[1] A. Hadjiprocopis and R. Linding. 'Systems Genetics, Linking Genotypes and Phenotypes'. In: ed. by F. Markowetz and M. Boutros. Cambridge Series in Systems Genetics. Cambridge University Press, 2015. Chap. Phenotype State Spaces and Strategies for Exploring Them, pp. 214–233.

BIOINFORMATICS

[2] T. Cox, G. Lang, A. Hadjiprocopis, D. Bird, K. Bennewith and J. Erler. 'Lysyl oxidase activity levels in the plasma are indicative of disease state and can predict patient outcome'. Submitted.

[3] J. Chang, M.-C. Djidja, M. Mrsnik, J. Sinclair, H. E. Barker, A. Hadjiprocopis, R. Linding, C. Jorgensen and J. Erler. 'Identification of hypoxia-regulated proteins using MALDI-Mass Spectrometry imaging combined with quantitative proteomics'. In: *J. Proteome Res.* 24.13 (5 May 2014), pp. 2297–313.

[4] N. Angelopoulos, A. Hadjiprocopis and M. D. Walkinshaw. 'Chemoinformatics and Advanced Machine Learning Perspectives: Complex Computational Methods and Collaborative Techniques'. In: ed. by H. Lodhi and Y. Yamanishi. Book Series on Chemoinformatics. IGI, 2011. Chap. Learning binding affinity from augmented high throuput screening data, pp. 212–234.

[5] N. Angelopoulos, A. Hadjiprocopis and M. D. Walkinshaw. 'Bayesian Model Averaging for Ligand Discovery'. In: *Journal of Chemical Information and Modeling* 49 (6 Jan. 2009), pp. 1547–1557.

NEUROLOGY

[6] W. Rashid, A. Hadjiprocopis, G. Davies, C. Griffin, D. Chard, M. Tiberio, D. Altmann, C. Wheeler-Kingshott, D. Tozer, A. Thompson and D. H. Miller. 'Longitudinal evaluation of clinically early relapsing-remitting multiple sclerosis with diffusion tensor imaging'. In: *Journal of Neurology* 255 (3 2008), pp. 390–7.

[7] G. R. Davies, A. Hadjiprocopis, D. R. Altmann, D. T. Chard, C. M. Griffin, W. Rashid, G. J. Parker, P. S. Tofts, R. Kapoor, A. J. Thompson and D. H. Miller. 'Normal-appearing grey and white matter T1 abnormality in early relapsing-remitting multiple sclerosis: a longitudinal study'. In: *Multiple Sclerosis* 13 (2 Mar. 2007), pp. 169–77.

[8] A. Hadjiprocopis, W. Rashid and P. Tofts. 'Unbiased segmentation of diffusion weighted Magnetic Resonance Images of the brain using iterative clustering'. In: *Magnetic Resonance Imaging* 23 (8 Oct. 2005), pp. 877–85.

[9] G. R. Davies, D. R. Altmann, A. Hadjiprocopis, W. Rashid, D. T. Chard, C. M. B. Griffin, P. S. Tofts, G. J. Barker, R. Kapoor, A. J. Thompson and D. H. Miller. 'Increasing normal-appearing grey and white matter magnetisation transfer ratio abnormality in early relapsing-remitting multiple sclerosis'. In: *Journal of Neurology* 252 (9 Sept. 2005), pp. 1037–44.

[10] G. R. Davies, L. Ramió-Torrentà, A. Hadjiprocopis, D. T. Chard, C. M. B. Griffin, W. Rashid, G. J. Barker, R. Kapoor, A. J. Thompson and D. H. Miller. 'Evidence for grey matter MTR abnormality in minimally disabled patients with early relapsing-remitting multiple sclerosis'. In: *Journal of Neurology, Neurosurgery and Psychiatry* 75 (7 July 2004), pp. 998–1002.

[11] S. J. Hickman, A. Hadjiprocopis, O. Coulon, D. H. Miller and G. J. Barker. 'Cervical spinal cord MTR histogram analysis in multiple sclerosis using a 3D acquisition and a B-spline active surface segmentation technique'. In: *Magnetic Resonance Imaging* 22.6 (2004), pp. 891–895.

[12] W. Rashid, A. Hadjiprocopis, C. M. Griffin, D. T. Chard, G. R. Davies, G. J. Barker, P. S. Tofts, A. J. Thompson and D. H. Miller. 'Diffusion tensor imaging of early relapsing-remitting multiple sclerosis with histogram analysis using automated segmentation and brain volume correction'. In: *Multiple Sclerosis* 10 (1 Feb. 2004), pp. 9–15.

[13] A. Hadjiprocopis and P. Tofts. 'An Automatic Lesion Segmentation Method for Fast Spin Echo Magnetic Resonance Images using an Ensemble of Neural Networks'. In: *IEEE International Workshop on Neural Networks for Signal Processing (NNSP)* (Sept. 2003).

[14] A. Hadjiprocopis and P. Tofts. 'Towards an Automatic Lesion Segmentation Method on FSE Images using an Ensemble of Neural Networks'. In: 11th *Scientific Meeting of the International Society for Magnetic Resonance in Medicine* (May 2003).

[15] A. Hadjiprocopis, R. Waqar and P. Tofts. 'Segmentation of T_2-weighted MRI using an Ensemble of Neural Networks and Clustering Experts'. In: 11th *Scientific Meeting of the International Society for Magnetic Resonance in Medicine* (May 2003).

[16] S. Hickman, A. Hadjiprocopis, O. Coulon, D. H. Miller and G. J. Barker. 'Spinal Cord MTR Histograms in Multiple Sclerosis Using a 3D Gradient Echo Acquisition'. In: 11th *Scientific Meeting of the International Society for Magnetic Resonance in Medicine* (May 2003).

[17] W. Rashid, A. Hadjiprocopis, C. M. Griffin, D. T. Chard, G. R. Davies, G. J. Barker, P. S. Tofts, A. J. Thompson and D. H. Miller. 'Investigation of early relapsing-remitting multiple sclerosis using diffusion MR histograms'. In: 11th *Scientific Meeting of the International Society for Magnetic Resonance in Medicine* (May 2003).

[18] A. Hadjiprocopis. *Segmentation of T_2-weighted MRI using entropy minimisation by simulated annealing.* Technical Report. NMR Research Unit, Institute of Neurology, London, UK, Dec. 2002.

IMAGE PROCESSING

[19] A. Hadjiprocopis, M. Ioannides, K. Wenzel, M. Rothermel, P. S. Johnsons, D. Fritsch, A. Doulamis, E. Protopapadakis, G. Kyriakaki, K. Makantasis, G. Weinlinger, M. Klein, D. Fellner, A. Stork and P. Santos. '4D reconstruction of the past: the image retrieval and 3D model construction pipeline'. In: *Proc. SPIE* 9229:922916-922916-10 (2014).

[20] A. Hadjiprocopis, K. Wenzel, M. Rothermel, M. Ioannides, D. Fritsch, M. Klein, P. S. Johnsons, G. Weinlinger, A. Doulamis, E. Protopapadakis, G. Kyriakaki, K. Makantasis, D. Fellner, A. Stork and P. Santos. 'Cloud-based 3D Reconstruction of Cultural Heritage Monuments using Open Access Image Repositories'. In: *Eurographics Workshop on Graphics and Cultural Heritage - Short Papers / Posters.* Ed. by R. Klein and P. Santos. The Eurographics Association, 2014.

[21] G. Kyriakaki, A. Doulamis, M. Ioannides, K. Makantasis, E. Protopapadakis and A. Hadjiprocopis. '4D Reconstruction of Tangible Cultural Heritage Objects from Web-Retrieved Images'. In: *International Journal of Heritage in the Digital Era* 3.2 (2014), pp. 431–452.

[22] A. Doulamis, M. Ioannides, N. Doulamis, A. Hadjiprocopis, D. Fritsch, O. Balet, M. Julien, E. Protopapadakis, K. Makantasis, G. Weinlinger, P. S. Johnsons, M. Klein, D. Fellner, A. Stork and P. Santos. '4D reconstruction of the past'. In: *Proc. SPIE* 8795:87950J-87950J-11 (2013).

[23] M. Ioannides, A. Hadjiprocopi, N. Doulamis, A. Doulamis, E. Protopapadakis, K. Makantasis, P. Santos, D. Fellner, A. Stork, O. Balet, M. Julien, G. Weinlinger, P. S. Johnson, M. Klein and D. Fritsch. 'Online 4D Reconstruction Using Multi-Images Available Under Open Access'. In: *ISPRS Annals of Photogrammetry, Remote Sensing and Spatial Information Sciences* 1 (July 2013). best paper award, pp. 169–174.

MACHINE LEARNING

[24] A. Hadjiprocopis and P. Smith. 'Feed Forward Neural Network Entities in Time Series Prediction and Image Classification'. In: *Proceeding of the International ICSC/IFAC Symposium on Neural Computation.* Vienna, 1998, pp. 1002–1008.

[25] A. Hadjiprocopis and P. Smith. 'Feed Forward Neural Network Entities'. In: *Lecture Notes in Computer Science: Biological and Artificial Computation: From Neuroscience to Technology.* Ed. by J. Mira, R. Moreno-Diaz and J. Cabestany. Springer–Verlag, 1997, pp. 349–359.

[26] A. Hadjiprocopis and P. Smith. 'Feed Forward Neural Network Entities in the analysis of high-dimensional data'. In: *Proceedings of the 3rd International Conference on Neural Networks and their Applications.* 1997, pp. 147–154.

[27] A. Hadjiprocopis, P. Smith, R. Comley and S. Lakkos. 'A Neural Network Scheme for Earthquake prediction based on the Seismic Electric Signals'. In: *IEEE Conference on Neural Networks and Signal Processing* (1994).

RESEARCH INTERESTS

<table>
<tr><td align="right">NAME:</td><td>**Andreas Hadjiprocopis**</td></tr>
<tr><td align="right">NATIONALITY:</td><td>**Cypriot** / **British** & **EU** passports</td></tr>
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RESEARCH PHILOSOPHY AND VISION :

I had been aware of Aristotle's maxim *the whole is greater than the sum of its parts* since high-school.

But I understood what it really meant when I saw Sun Microsystem's "*the network is the computer*" poster on a wall, at University. That made a lasting impression on me and quickly drew me into a different computational universe than the one already collapsing around me then such as the Fifth-Generation Project, Expert Systems, Minsky's Schemata and Frames and other *top-down, centrally controlled* behemoths.

Ever since – in my academic career – I have always been an ardent proponent of *Connectionism* and *Emergence*; *bottom-up* processes and systems in which the *inter-connections* and *interactions* between lots of simple units are much more important than the individual capabilities of each unit in achieving complex behaviour; the ants and the bees is a classic example.

My research philosophy is based upon the following notions:

i. Connectionism or *the whole is greater than the sum of its parts*. The collapse of the effort to build top-down AI systems, e.g. expert systems, has renewed the interest in bottom-up systems where the power of computation lies not on the power of computing elements but on their interconnections – *the network is the computer*. Since then, other non-classical AI techniques inspired by nature have become widely available due to the extraordinary development of computer systems – evolutionary and natural computation (genetic algorithms, swarms, ant colony optimisation, etc.), simulated annealing and Monte Carlo techniques, random fields, distributed computing, agents.

ii. Data integration and data fusion. The more views of the same thing the better.

iii. Open systems, modular design, reuse, public domain software.

PhD RESEARCH, MODULAR NEURAL NETWORK ARCHITECTURES :

During my bachelor's degree, I had developed an interest in the subject of **Feed Forward Neural Networks** (FFNN) and, in particular, their application to problem domains associated with data of high dimensionality: how can they really be parallelised, how can they interact with the real world, and lots of them too, without central control?

The application of FFNN to tasks involving high-dimensional data presents problems which emanate from the fact that these networks can not be scaled up unreservedly without serious side effects. For example, the volume of the space of possible solutions increases exponentially with the number of degrees of freedom of the FFNN (*curse of dimensionality*) which usually depends on the size and dimensions of the data at hand. Furthermore, the appearance of numerous local minima due to the increased complexity and multi-modality of the error surface associated with such data reduces the possibility of reaching the solution corresponding to the global minimum.

This was the subject of my research during my Ph.D. My thesis, entitled "*Feed Forward Neural Network Entities*", describes a methodology for replacing a single neural network with an *entity* of simpler and smaller FFNN, [1] – *a network of neural networks*. I proved mathematically that Feed Forward Neural

Network Entities (FFNNE), [3], are Universal Function Approximators (as they satisfy the criteria of the *Stone-Weierstrass* theorem) and can safely replace a monolithic neural network when the number of dimensions of the input data is prohibitively large for the latter.

Both FFNNE and single FFNN can be parallelised naturally due to their architecture. However, the fine-grain parallelism of a single FFNN is impractical, especially when a large number of neurons is involved because of huge message-passing and the fact that the processing requirements of a neuron are minimal. The FFNNE offer a coarse-grain parallelism which is more suitable to today's hardware. In other words, the FFNNE can be parallelised naturally and much more efficiently over a CPU farm.

As proof of concept, I had developed a script language and interpreter, in *perl*, for training FFNNE with the ability to distribute transparently a FFNNE over a number of desktop computers, thus reaping the benefits of FFNNE's coarse-grain parallelism using commonly available hardware.

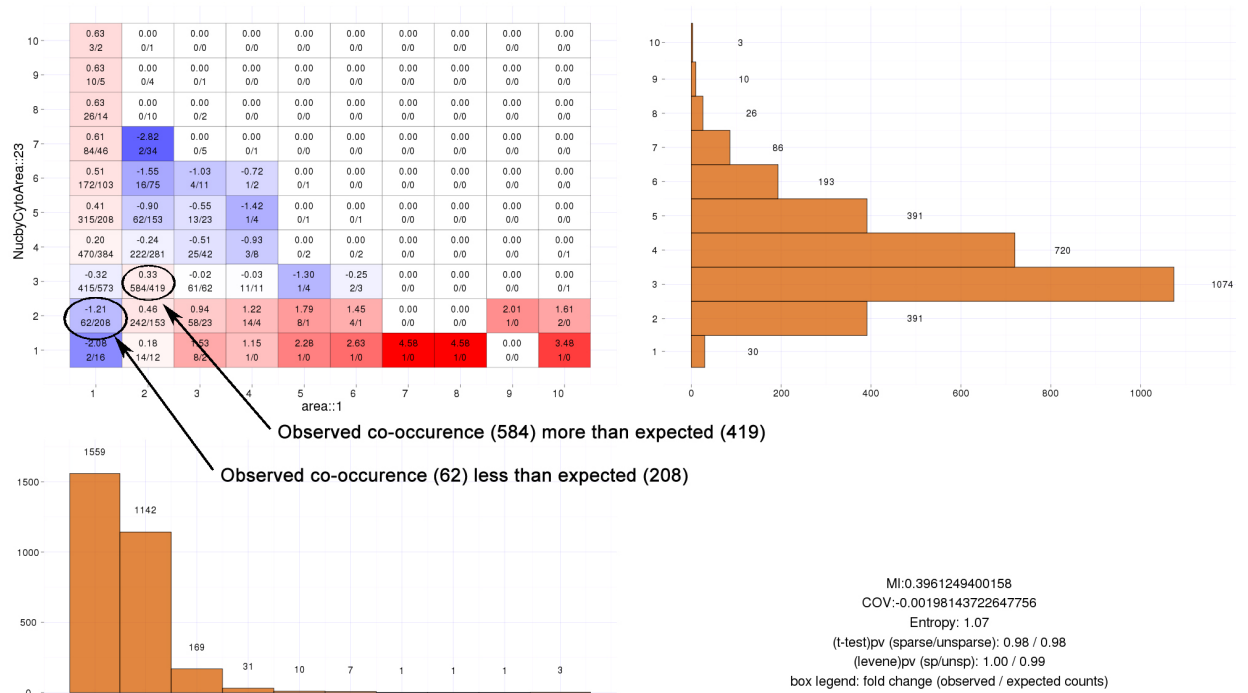HIGH THROUGHPUT CELL IMAGING & ANALYSIS :

At the Institute of Cancer Research, London (2009–2013) in association with Dr Chris Bakal who provided a large set of cell morphological, texture and stain intensity features available over a large number of cell lines, different treatment conditions and durations as well as growth media. This project deals with the analysis of geometrical and texture features extracted from single-cell images obtained from the OPERA HIGH-THROUGHPUT MICROSCOPE[1].
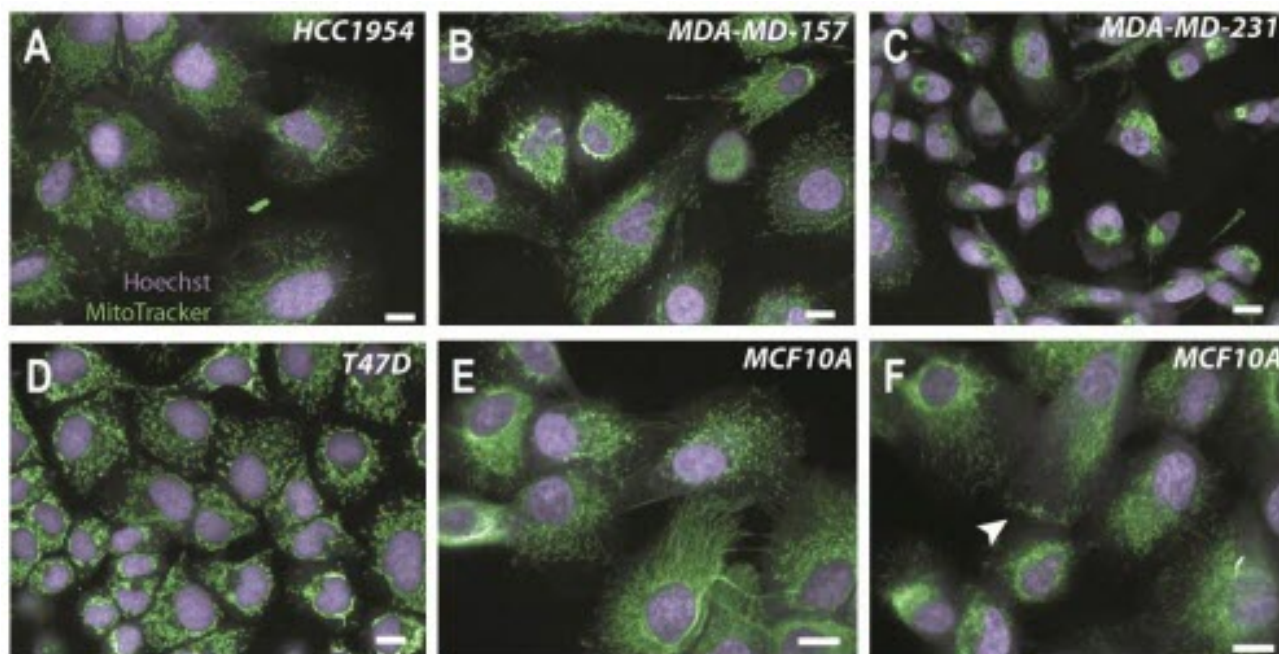
The analysis is done using the SGI ALTIX UV (512 cores, 4TB memory) supercomputer with the pipeline designed and implemented (including parallelisation for the supercomputer and use of shared memory, where possible) by myself (C, perl, bash). Here is an outline of my work in this area:

1. Implement parallelisable, robust statistical significance tests of population statistics differences using resampling methods, e.g. Permutation Tests, Monte Carlo, Bootstrap. (see `http://nfkb.scienceontheweb.net/differences_in_statistics/index.html`)

2. Assess separability of cell populations under different conditions (e.g. Hypoxia versus Air) based on their features and using bootstrap and Support Vector Machines or Fuzzy Clustering. (see `http://nfkb.scienceontheweb.net/separability_of_conditions/index.html`)

3. Highlight ranges of values of pairs of features whose co-occurrence deviates from what is expected according to the individual feature values distribution and if they are statistically independent.

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[1]From PerkinElmer, `http://www.perkinelmer.com/pages/020/cellularimaging/products/opera.xhtml`.

Observed co-occurence (584) more than expected (419)

Observed co-occurence (62) less than expected (208)

MI:0.3961249400158
COV:-0.00198143722647756
Entropy: 1.07
(t-test)pv (sparse/unsparse): 0.98 / 0.98
(levene)pv (sp/unsp): 1.00 / 0.99
box legend: fold change (observed / expected counts)
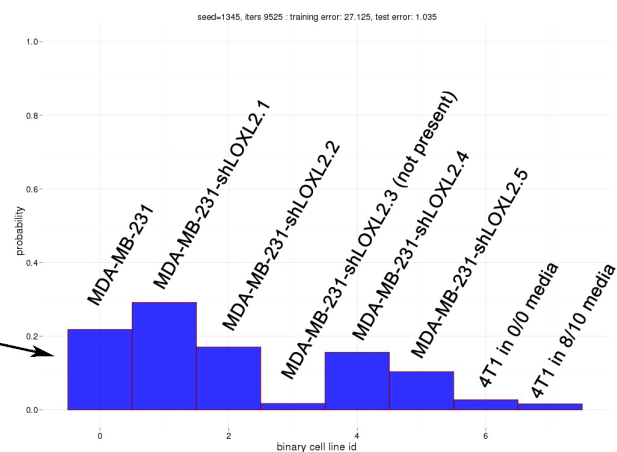
(see http://nfkb.scienceontheweb.net/sca/index.html)

4. Train Feed Forward Neural Network (FFNN) and FFNN Entities[2] to predict cell-line, treatment conditions and expression of NFκB in the nucleus and cytoplasm, using the feature values of individual cells as input.

5. These trained networks may serve as analytical models describing how different cell lines, treatment conditions or the expression of proteins (e.g. NFκB) correlate with feature values. Although neural network models contain thousands of parameters and thus it is impractical to infer high-level relationships within the data learned, simulations can help us put together a set of signature features that differentiate between the various cell lines and treatments. A simple way to do this is to create in-silico, artificial "cells" whose features except one are drawn randomly from their corresponding observed distribution[3]. The one feature left out is varied incrementally over its range. The trained neural networks then make a prediction of cell line / treatment given the observed values of features, for each of these artificial "cells". Thus we can see how this prediction varies with the one feature left out. For example, it was observed that for small values of feature *ruffliness*, the predicted cell lines were predominantly 'MDA-MB-231' *and* its five shLOXL2 variants. However as the values of that feature became larger, the prediction was predominantly for 'MDA-MB-231' *only*. See how the cell-lines on the left vary as *ruffliness* values increases.

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[2]A. Hadjiprocopis and P. Smith. "Feed Forward Neural Network Entities". In: *Lecture Notes in Computer Science: Biological and Artificial Computation: From Neuroscience to Technology.* Ed. by J. Mira, R. Moreno-Diaz, and J. Cabestany. Springer–Verlag, 1997, pp. 349–359.

[3]The observed data from one or more features is used to build one- or multi-dimensional Gaussian mixture models which can then supply random feature values. The accuracy of the mixture models depends on the available data which is by all standards, huge and covers two or three dimensions adequately.
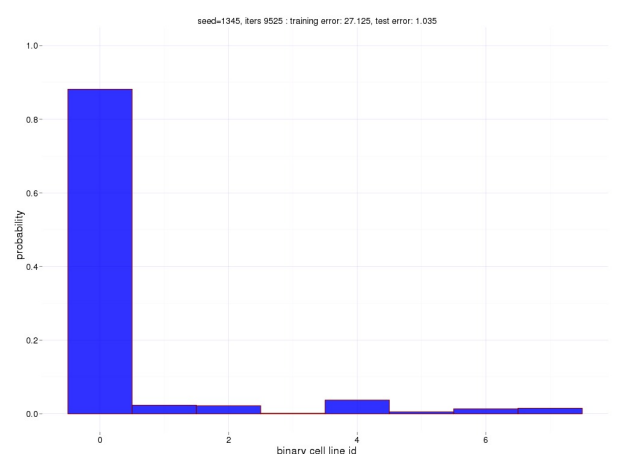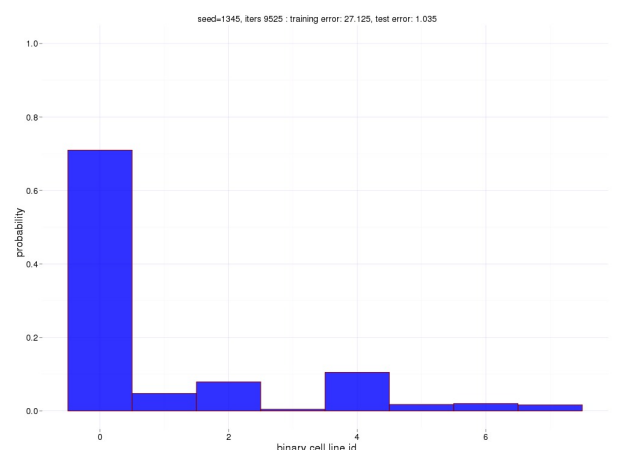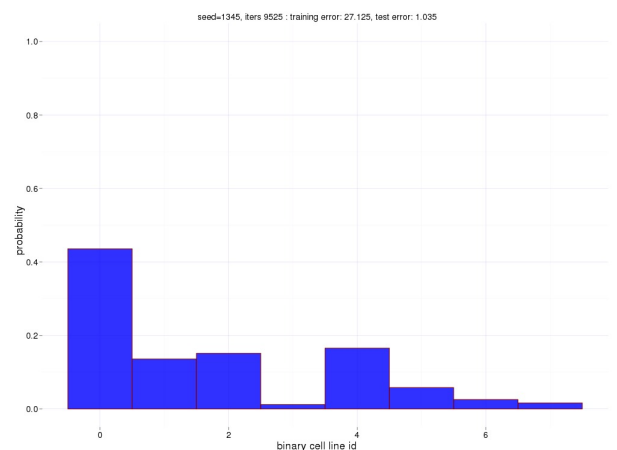
(see http://nfkb.scienceontheweb.net/predict_nfkb_or_cell_line/index.html)

4

<u>CELLULAR NOISE & ROBUSTNESS</u> :

I am interested in how best cellular processes can be modelled in order to capture their dynamic nature. I am also keen to investigate the effect of intracellular noise on these processes and why the phenotypes they lead to are still so robust. Below are some extracts from [9], a book chapter I have co-authored with Dr Rune Linding on *Systems Genetics, Linking Genotype and Phenotypes* (Cambridge Series in Systems Genetics) which best summarises my views:

Proteins and their interactions determine how cells behave. Genes are the blueprints for protein synthesis; their activation or suppression determines the absence or presence of a protein which can give rise to further activation or suppression of other genes. This chemical chain reaction usually involves positive and negative feedback loops and is subjected to stochastic noise and the influence of often unpredictable environmental factors. Moreover, epistasis - the cancellation or modification of a gene's contribution to the phenotype by other genes - is generally the rule rather than the exception in genetics.

Despite all these, amazingly robust cell behaviour is manifested although it is difficult to be modelled and predicted with traditional methods. Building the topology and quantifying the direct and indirect cause-effect (stimulus, expression, activation, behaviour) relationships of the reactions leading to the phenotypes - in general, genetic regulatory networks - is challenging in at least three ways.

Firstly, how these relationships are described; traditionally, mathematical models in terms of transfer functions relating inputs to outputs expressed as a composition of differential equations with a time dimension have been utilised. We argue though that the cellular signalling networks are probabilistic in nature and that diffusion based models remain challenging due to lack of knowledge of essential system parameters, such as rate constants.

Most importantly, treating intracellular protein and gene interactions as chemical reactions under the usual assumption of diffusion dynamics namely that of the free movement of a large number of molecules can not be safe. These interactions happen between a very small number of molecules in the confined space defined by the cell membrane which resembles less a liquid than a solid state therefore leading to significant statistical fluctuations in the behaviour of the reactions.

More recently, computational models in the form of Boolean networks, Petri nets, Interacting (Probabilistic) State Machines have been proposed [8] as an alternative way of modelling biological processes with the added benefits of abstraction, high-level reasoning and mature process calculus tools to aid analysis.

Secondly, our ability to gain understanding and abstract from derived molecular mechanisms and regulatory networks topology is really limited because of the sheer complexity and abundance of low level information inherent in these networks. In this respect, a way to reduce complexity is by treating the parts of these networks where the interactions within are much larger compared to the interactions between, as semi-autonomous modules - essentially, as black boxes. Modular response analysis [7] offers such a framework. Building on this, [15] developed a methodology for reverse engineering network structure in order to analyse how perturbations propagate in a network. Modularisation at a higher level is also key for reusing parts of the derived regulatory networks.

Thirdly, kinase activation can initiate different cellular decisions depending on the pre-activation state of the network. In [10], it was shown that JNK activation can be anti- or pro-apoptotic depending on network state when cells received growth factor cues. Therefore, to describe and predict a cellular response to a perturbation, studies must be carried out in the context of the cell's multivariate network state [11].

Genotype can be seen as a set of instructions carried within an organism's genetic code, the DNA. This is straight-forward. Phenotype's definition however is an example of constructive generality. Is something which is observable, important to the life of that individual or others around it? Is something

which is important, observable and / or measurable, at what temporal and spatial scales and over what population size?

Additionally, many cell processes are oscillatory. The frequency and amplitude of these oscillations as well as other qualitative characteristics, may also be characterised as phenotype. When single cells are studied individually, these oscillations are observed. However, when a population of cells is studied as a whole, via, say a Western blot, it is quite possible that the observed result of these processes averages to some behaviour that does not exist at all anywhere in the population, [6]. It is also quite possible that for some of these processes, depending on cell (a)synchronicity, that the observed average over a population is total inactivity, whereas each single cell of the population is quite active in itself, [14].

ANALYSIS OF MALDI SPECTRA FUSED WITH MICROSCOPY TISSUE IMAGES :

This work was conducted at the Institute of Cancer Research, London (2009–2013), in association with Dr Janine Erler. It uses tools from my previous work at the Institute of Neurology, London where various modalities of brain MRI images were put together and an ensemble of classifiers were trained to identify lesions (multiple sclerosis). In this case we try to identify cancer tumours and hypoxic regions in tissue.

The MALDI (matrix-assisted laser desorption/ionization) provides a list of biomolecules for each square of a grid of relatively high resolution for slices of tissue. This information is combined with microscope images of neighbouring tissue slices (above or below), possibly stained, and tumour or Hypoxic regions outlined by an expert. Neural networks are trained to identify tumour areas and clustering is performed to see the separability of tumour and non-tumour areas.

PROTEOMICS: ANALYSIS OF SILAC LABELLED MASS-SPECTROMETRY / MICRO-ARRAY :

At the Institute of Cancer Research, London (2009–2013), in association with Prof. Chris Marshall and Dr Janine Erler, who provided microarray and mass spectrometry data.

This is about building protein-protein interaction networks from the proteins detected by MS and/or micro-array by integrating the results with public databases such as STRING for protein interactions and GO for gene function and other information. The novelty lies in handling the constructed network graph which consists of first- and second-degree neighbours to detected proteins. Such a network is very large but can be handled with distributed graph searching algorithms.

Protein complexes are either identified using clustering on STRING data or loaded from other public databases. Cluster deviations from network mean are identified and their statistical significance is assessed using resampling statistics methods.

Undetected proteins (e.g. those first- and second-degree neighbours to detected proteins) which may be hubs or otherwise be important if detected can easily be identified and experiments setup to investigate their expression further.

For the first phase of this project, I wrote software (in R, C, perl, bash) to interrogate online public databases such as protein name translations (e.g. `ensembl` ↔ `affymmetrix` ↔ `hugo`) and protein interactions (e.g. `string-db`) or to export significant proteins as a (`Cytoscape`) network. Although a major challenge, this part is routine.

During the second phase of the project, I have developed a procedure for exploring interactors to bridge groups of significant activity as reported by the microarray or mass spectrometer. This procedure builds a network using databases of protein interactions and finds shortest paths between groups of proteins which have not been linked experimentally. This allows the experimenter to verify interesting "bridges".

MEDICAL IMAGE PROCESSING :

The results of my PhD research were applied to my work at the **Institute of Neurology, London** (2001–2004). In particular, I used FFNN and FFNNE for the **detection of Multiple Sclerosis** (MS) **lesions** in

Magnetic Resonance Imaging (MRI and functional MRI – DTI) brain scans. Our methodology utilises FFNNE trained with data from images of different contrast and selected using variable criteria (e.g. location, voxel intensity, texture, *etc*), [4].

Another task I was dealing with at the Institute of Neurology was the **segmentation of MRI brain scans** in three compartments, namely *white matter*, *gray matter* and *cerebrospinal fluid*. To this end, I have used neural networks and clustering techniques with relative success, [5]. In addition, a second method for dealing with the task of brain segmentation was sought. The problem of segmentation was reformulated as a problem of optimisation where it is required to minimise the entropy of the set of probabilities of assignment of a voxel to each of the three compartments. The process of minimisation is undertaken by **Simulated Annealing**, [2]. As a future plan, Simulated Annealing can be replaced by the technique known as Markov Chain Monte Carlo.

I have also participated in the analysis of **Cervical Spinal Cord Magnetic Transfer Ratio** (MTR) of patients with MS, [13].

As a future plan, it would be interesting to investigate the use of Cellular Automata to tasks of image segmentation and data clustering.

GENERAL PURPOSE COMPUTATION USING GRAPHICS HARDWARE :

Today's graphics hardware (GPU) are designed to take advantage of the inherent parallelism in graphics calculations as well as the fact that these calculations involve huge arrays of data. Modern GPUs consist of a number of lightweight, multi-threaded processing elements executing code concurrently. The result is a device which does matrix arithmetic very efficiently.

Lately, GPU manufacturers have encouraged the use of their graphics hardware for general purposes by providing development tools and information. GPUs seem to be a cheap and effective solution for high performance computing, thus giving a desktop computer cluster computing capabilities.

I am interested in utilising GPUs for high performance computing for scientific purposes [12] – for example in the areas of neural networks, visualisation and virtual reality, simulation of physical systems (artificial life, evolution of ecosystems), human simulation – e.g. a crowd in a train station.

Recently, in order to support my research, NVIDIA has kindly donated to me two cutting-edge graphic processing cards (K20, TESLA GPU). This hardware can deliver 2 Tflops of processing power when fully exploited[4]. Certainly, not all algorithms are suited for SINGLE INSTRUCTION MULTIPLE DATA (SIMD) processing but Feed Forward Neural Networks, Permutation Tests, Support Vector Machines and Fuzzy Clustering all show tremendous speedups when compared to running on traditional **CPU** machines which means that the use of a regular supercomputer is not strictly necessary for crunching biological data. The GPU hardware will have central role in the proposed lab and I believe that with proper algorithm implementations it can become a desktop super-computer.

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