

“ProcellEvolution”

STARTPAGE

HUMAN RESOURCES AND MOBILITY (HRM)
ACTIVITY

MARIE CURIE ACTIONS
Marie Curie Intra-European Fellowships (EIF)

PART B Section 1

“ProcellEvolution”

B1.1 SCIENTIFIC QUALITY OF THE PROJECT (MAXIMUM 4 PAGES)

Scientific/Technological quality, including any interdisciplinary and multidisciplinary aspects of the proposal.

The origin of life remains a mystery due to a number of *apparent* Ouroboric paradoxes. The first apparent paradox is, if metabolism is necessary to produce nucleic acid template replicators, but nucleic acid template replicators are necessary for the evolution of metabolism, which came first? The second apparent paradox is, if protein enzymes are necessary to replicate DNA, but DNA is necessary to encode protein enzymes, which came first? Although solutions can be envisaged, crucial details are lacking from both.

It is not known how the evolutionary machinery that allowed unlimited heredity, i.e. long nucleic acid template replication, could have arisen, because nucleotides are very complex molecules that must be synthesised from simpler precursor molecules by metabolism. Even proponents of the RNA world hypothesis admit that considerable evolution must have taken place to obtain RNA¹. However, we do not understand how metabolism, a necessary pre-requisite for the origin of an abundant biosphere capable of sustaining units of evolution (Ganti, 2003), (Szathmary et al, 2005), could have arisen prior to the encoded catalysis and microevolution afforded by template replicators (ref). A complex autocatalytic metabolism cannot arise by chance (King,). The pre-biotic synthesis experiments of Stanley and Miller demonstrate the capacity for the formation of a combinatorial explosion of organic molecules (tar), but stop short of suggesting the recipe for turning this tar into life (Stanley, Miller).

In aid come two main alternatives. Could standard template based evolution have operated using *spontaneously occurring* clay crystal templates that co-evolved with a metabolism that produced nucleic acid products (Cairns-Smith, 1982, Orgel 2003)? If this view is true, sequence based modular information transmission was mediated by clay instead of nucleic acids, and selection was between alternative adjacent proliferating organizations. Although there is evidence that clay minerals promote oligomer and ribose phosphate formation by the formose reaction (Ferris, 2002), there is no demonstration as yet that clay crystals can act as the informational subsystem of a unit of evolution. Alternatively, it is proposed that metabolic networks could have undergone attractor-based evolution on pyrite surfaces (Wächtershäuser, 1982). However, objections to such a mechanism arise due to the lack of any convincing theory (Orgel, 2000) of how sufficient heredity could be sustained by chemical networks capable of ‘merely’ holistic inheritance in a well mixed reactor or even on a surface (Szathmary,). The first component of this proposal seeks to understand the earliest major transitions that occurred in pre-genetic chemical systems (Maynard-Smith & Szathmary, 1997), in particular, what capacity evolution had to act on chemical networks, rather than on templates.

In answer to the second paradox, the RNA world was proposed. However, although *in vitro* selection of ribozymes, (Cech, 1986a,b), (McGinness & Joyce, 2003) lends credence to the idea of an intermediate RNA world (Gilbert, 1986), we still have no replicase ribozyme (Johnston, 2001) . Non-enzymatic synthesis of templates up to 55 nucleotides has been achieved on mineral surfaces (Ferris et al 1996), but there is no replication, because templates do not recycle by unzipping (Kovac et al 2003). Short oligonucleotide analogues can self-replicate (Von Kiedrowski, 1986) (Sievers & Von Kiedrowski, 1994), but longer ones cannot because self-inhibition by strand association becomes prohibitive. Whereas today, ATP driven enzyme mediated reactions are

¹ Orgel, L. & Lohrmann, R. (1974). Prebiotic chemistry and nucleic acid replication. *Accounts of Chemical Research*, 7, 368–. Orgel, L. (2004). Prebiotic chemistry and the origin of the rna world. *Crit. Rev. Bioch. Molr. Biol.*, 39, 99–.

responsible for forcing strand separation during DNA and RNA replication, these would have been unavailable for the relief of primordial product inhibition. One proposed solution is for the reactor to supply the energy required for intermittent denaturation, for example by tidal cycling (Lathe, 2005) or high-temperature spikes from a low temperature baseline, however, it can be easily appreciated that denaturation spikes alone are insufficient to achieve replication because **elongation side-reactions** are equally prevalent during the renaturation phase as in the baseline condition, so that although product inhibition is relieved, elongation side reactions still poison template replication, see figure 1.

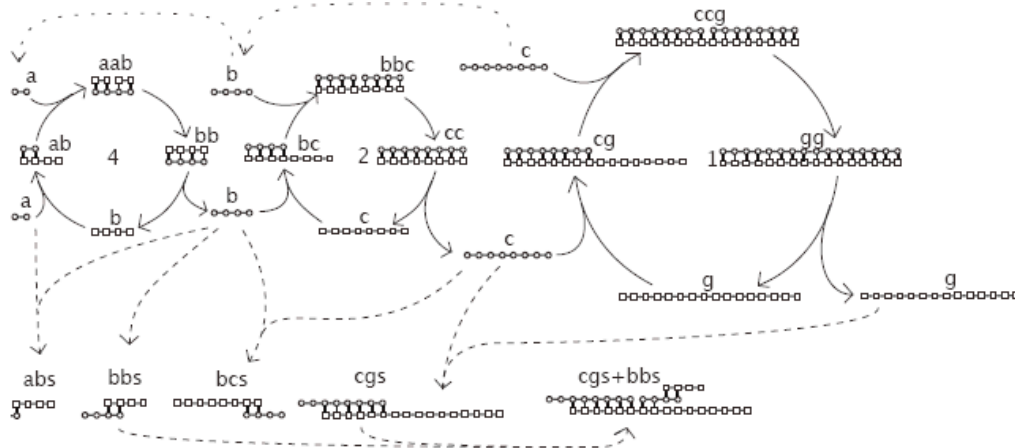


Figure 1. 3 coupled autocatalytic cycles of template replication. Templates are of length a, b, and c, each twice the length of the previous template. Elongating side reactions tap each cycle, depleting the coupled flux from left to right.

One way around this problem is hinted at by the experiments of Zielinski and Orgel (Zielinski and Orgel, 1987a, 1987b, 1989), who showed that considerable phenotypic diversity exists even for tetramers, due to stacking effects acting beyond the nearest neighbor (Cruz, 1982) that influence whether a perfect or a staggered duplex is formed (Sinclair, 1984), for example, GCGC is capable of replication due to the formation of perfect duplexes, whereas CGCG elongates by joining of staggered duplexes at splint junctions. What is the minimal (shortest) RNA ribozyme capable of extricating itself from the curse of elongating side-reactions? Could some sequences exploit an oscillating reactor better than others, to achieve their self-replication? An alternative to an oscillating reactor was proposed by Ganti, in which product inhibition may be relieved if a motif is capable of folding up onto itself under certain conditions (Ganti, 2003). All that remains is that the sequence be able to accept complementary oligomers and reform the double strand under some alternative reactor conditions. One problem with this mechanism of replication is that it is sequence dependent; therefore it would not immediately increase the capacity for information transmission. Also, in addition to the self-zipping mechanism, the sequence motif would also need to cut itself out or prevent the formation of overlapping staggered ends that would enslave the sequence motif within an elongating polymer (as implied by figure 1).

The functionality of the **minimal replicase ribozyme** is not known. By ‘minimal replicase’ we mean, the shortest ribozyme of length N that can allow replication of sequences of length $N+1$ with sufficient fidelity for evolution of ribozymes of length $N+1$. To explain the origin of the minimal replicase ribozyme, by definition, requires a non-enzymatic explanation, since if a ribozyme had been necessary, then *that* would be the minimal replicase ribozyme. It is unlikely that the replicase ribozymes based on a processive ligase design being explored by Johnston and others (Johnston, 2001, Eklund, 1995, McGinness & Joyce, 2003) could constitute a minimal repliase ribozyme because: i) such ribozymes are too long (> 100 nucleotides in length) to have been capable of

evolution in the absence of some other ribozyme or mechanism, and ii) if ligation is the primary problem *preventing* replication due to the entrapment of nucleotides into templates undergoing runaway elongation, such ribozymes would not have been helpful at this stage in any case.

Research Methodology

We will develop and extend computational models of three poorly understood phases of evolution.

1. Pre-biotic Formose cycle based chemical networks capable of protocell formation.
2. Protocells containing already complex metabolic networks (Benner 1999, Jeffares, *et al.* 1998), capable of evolving templates.
3. Evolution of non-enzymatic long nucleic acid template replication, and the origin of the minimal replicase ribozyme.

Consequently, the proposed project combines chemistry (organic chemistry and reaction kinetics), biology (evolutionary biology and molecular biology) and computer science (method).

Method 1: Replicator network dynamics have been explored for Lotka-Volterra equations and replicator equations by community iteration methods (May)(Law)(Stadler). Although many artificial chemistry models of chemical evolution exist, they cannot be used to assess the probability of increasingly complex autocatalytic cycle formation (ref)(Fontana). Although a lot of hype was generated (ref) about models of the emergence of protein or RNA based autocatalytic sets by Stuart Kauffman (ref), they do not acknowledge the existence of catalytic poisons, they assume the existence of an underlying metabolic network that produces catalytic templates in the first place, and so far no autocatalytic set is known to exist (ref). None of the above models gives guidance that would be of any use to a practical chemist about what they have to do in order to observe increasingly complex supra-chemical systems subject to evolution, in their laboratory. The dynamics of a network of chemical intermediates is quite distinct from the dynamics of the above networks. Firstly, interactions between chemical species are productive, i.e. stoichiometrically determined, not catalytically determined. Secondly, flows of matter through the network are subject to thermodynamic constraints, i.e. if a conservative system is being modeled, evolution cannot change the kinetics of the network arbitrarily. This assumption is often omitted in models of the evolution of chemical networks; therefore introducing the erroneous implicit assumption that external energy sources can be utilized at will to alter the equilibrium position of any reaction. Thirdly, the vast platonic chemical space is explored non-ergodically and contains niches that are occupied to varying degrees by matter. There is great heterogeneity to be found in the reaction topology of chemical niches. For example, in some niches, compound X may be able to undergo a wide range of addition reactions that specifically block different active sites. There may exist favorable niches in chemical space that are capable of mediating a high degree of holistic heredity.

Stochastic models of the evolution of metabolism, subject to the above constraints, in a closed thermodynamic system, have been produced (Fernando, 2005). We found that stochastic methods were too inefficient to simulate a sufficiently large and interesting chemical space. Therefore, in this proposal we will use a community iteration method, simulating a moving “window” in chemical space, to explore how matter discovers chemical niches within that space. Rules will be produced that define the stoichiometric matrix (ref), thermodynamics and kinetics of transition to the adjacent possible chemical space. We hope to understand how the nature of the chemical transition rules and the capacity for re-cycling of high free-energy matter by abiotic processes, influences the ability for matter to discover chemical niches in which higher-order chemical organizations (ref) can arise.

Method 2: Deterministic chemical kinetic and stochastic models of whole protocell dynamics have been produced in order to understand the conditions in which template replication may evolve in protocells (Fernando, 2004) (Fernando, 2005). By increasing the realism of the metabolic model, i.e. including side-reactions, an inherent polymer production mechanism, and incorporating a more realistic model of polymer dynamics (see methods 3), we wish to explore whether protocells would evolve template replication.

Method 3: Previous models of the origin of nucleic acid replication have consisted of ordinary differential equation models that incorporate high-level chemical assumptions^{13,14,15}, such as direct chain growth¹⁷, sub-exponential or parabolic template growth rates in a closed system¹⁶, ribozyme effects, or postulate specific replication mechanisms¹⁸. Macroscopic physical models of template replication, although relaxing these assumptions, do not embody the order of magnitude differences in rates between phosphodiester-bond (p-bond) and Watson-Crick base pair (h-bond) events observed in nucleic acids, and have not demonstrated *long* template replication^{19,20}. In order to integrate these diverse approaches, a low-level stochastic model of the underlying chemical kinetics of nucleotide and polymer dynamics was designed to explore the sufficient functional conditions for non-enzymatic long template replication. Major obstacles encountered were: i) the vast number of distinct configurations that nucleic acid polymers can adopt transiently, resulting in many possible types of interaction, ii) the order-of magnitude difference in characteristic time scales between Watson-Crick base-pairs (h-bonds) and phosphodiester bonds (p-bonds); and iii) the high interdependency of reaction rates, due to hydrogen bond stacking interactions, and inter-polymer reactions. These problems were solved respectively by i) limiting the secondary structures to a 2D square grid, and simulating only very small volumes containing only a few templates ii) using a relaxation method to allow h-bond dynamics to run approximately to equilibrium before each p-bond event, and iii) using a very efficient stochastic algorithm^{21,34}. Realistic reaction kinetics and free energies were obtained from empirical studies^{22,23,24,25,26,27,28}. Our stochastic model now incorporates the nucleotides A, C, G, and T, and realistically simulates stacking effects. We have also been able to simulate ribozyme particles, that act upon hydrogen and phosphodiester bonds.

Using this simulation, we have already identified two main obstacles to replication of long strands: (i) competition by successfully replicating short templates; and (ii) creation of new short templates by premature detachment of incomplete copies from longer strands. We showed that these obstacles could be overcome by; high polymer concentration, low monomer concentration, and low temperature. However, under these conditions, runaway elongation was found to compete with replication. Although elongation could be prevented, to some extent, by sequence specific stacking effects, such as those allowing GCGC to replicate^{8,9}, yet causing CGCG to elongate^{10,11}, we showed that this mechanism was insufficient to allow long sequence replication. Temperature oscillation alone¹¹ was insufficient to allow long nucleic acid replication, since this did not favourably alter the flux ratio between the replication and elongation pathway. Furthermore, no ligase ribozyme could be designed that was capable of achieving replication, without the capacity for processivity.

I am currently working in collaboration with Guenter Von Kiedrowski's team (Ruhr-University Bochum), who have encountered the same problem of runaway elongation side-reactions, in DNA analogous replicating by formation of phosphoamidate bonds. In this project I will incorporate more complex secondary structures into my model, e.g. hairpins. A simulation of RNA at the level of detail of the co-fold algorithm (ref) would be too slow to allow modelling of populations of RNA interactions, and so I seek a valid algorithm that captures some of the crucial catalytic capacities of RNA necessary for the minimal replicase ribozyme.

Originality and innovative nature of the Project and relationship to the state of the art in the research field

Our first novel hypothesis is that the notoriously diverse (Orgel,) set of chemical super-systems based on formose cycle autocatalytic cores (Deamer), can be maintained, with selection and variation between members of the set. The cores occupy a heterogeneous mineral surface with a variety of abiotic catalytic effects, pressures, temperatures, gas phase compositions, external energy sources and hence varied capacities for chemical re-cycling. We predict that chemical niche construction by simple autocatalytic structures to produce more complex organizations with lower decay rates would have been selected for (Fernando, 2005) (ref Niche Construction people). An important factor allowing this, we propose, was the capacity for some metabolic cores, in an initially narrow range of abiotic catalytic environments, to form encapsulating membranes, such that syncytia could form (Ono,), allowing a vectorial metabolism (ref) limiting lateral diffusion of chemicals, conferring selective permeability, and allowing energy transduction (Kepa). Such a primitive membrane could limit the entry of ‘poisons’ that could drain the autocatalytic core, and increase the internal concentration of substrates. This process we call the *progressive sequestration* by metabolism of metabolism. The concept of selection for ‘chemical ecosystems’ is partially analogous to ecosystem level selection (Alex)(Slone Wilson) in which the community composition of replicators is selected for. An understanding of chemical evolution requires study of the dynamics of evolution in continuous (multi-dimensional) systems in which discrete ‘units of selection’ are not defined. The way that evolution works in such systems is extremely poorly understood, but may well be pertinent to the dynamics of various complex organizations. Using method 1, this hypothesis will be elaborated.

Our second novel hypothesis arises from the fact that the protocell scenario immediately suggests a source of selective pressure for the origin of nucleic acid template replication. Some side-products of the formose cycle core would undergo polymerization and become trapped within the protocell (Ganti,). Selection at the protocell level may initially have been on the basis of the stoichio-kinetic effects of such products on protocell replication rate (Ganti, 2003). I have developed models that show that in a protocell in which membrane molecule production depends on the production of charged molecules produced during template polycondensation reactions, that there is a detrimental effect of unbounded template elongation due to two factors that limit the rate of polycondensation; i) equilibrium template concentration is decreased, ii) product inhibition reduces the extent of single stranded template regions available for polycondensation (Fernando, 2005). In contrast, a protocell capable of maintaining a template population that has melting temperatures approximately equal to the ambient temperature, experiences the greatest rate of polycondensation reactions, and hence has the greatest replication rate. Note that this selective pressure does not depend on any catalytic advantage conferred by templates. However, sequence and nucleotide composition may have been selected for, *independently of any catalytic effect of sequences*, since template sequence and nucleotide composition influence melting temperature. Using method 2, this hypothesis will be elaborated.

The third novel hypothesis is that protocells could provide a cyclic environment coupled to the cell cycle, capable of intermittent denaturation of long templates. Many sequences would undergo elongation upon renaturation. However, we propose that due to the diversity of sequence specific folding properties available to RNA, selection would be able to discover sequence motifs capable of self-folding, or restriction activity, capable of protecting them from becoming trapped in elongating strands. Using method 3, this hypothesis will be elaborated.

Timeliness and relevance of the project

The project is timely because advances in computer science have resulted in parallel algorithms for the exact stochastic simulation of chemical systems distributed in space (Elf) (Ono). Evolutionary and autocatalytic dynamics are influenced by spatial structure (Scherring) (King). The widespread nature of epigenetic inheritance mechanisms has been appreciated (Jablonka) (jablonka). A timely symmetry would be established by elucidating the mechanisms of pre-genetic inheritance. Similar evolutionary dynamics can be expected to produce novel units of evolution and novel informational inheritance systems in ecological and cultural network organizations today.

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BI.2 QUALITY OF THE RESEARCHER

Summery of Major Achievements and Suitability for the Project

I obtained a 1st class honours degree in physiological sciences (B.A) and a medical degree (B.M. B.Ch) at Wadham College, Oxford. I practiced as a 'house officer' (junior doctor) in general medicine and general surgery for a year at the John Radcliffe Hospital, and became registered with the General Medicine Council in the year 2000. Although offered an S.H.O training rotation in psychiatry at Oxford, I opted to pursue my interest in theoretical neuroscience by carrying out an

MSc in Evolutionary and Adaptive Systems at Sussex, where I used artificial evolution to explore self-organizing algorithms in recurrent neural networks controlling robots to carry out learning in multiple T-maze tasks. At Sussex, I was first author on a prize-winning paper in which we constructed a liquid state machine (a model of a cortical microcolumn) out of a bucket of water. I completed work on my DPhil in computer science in early 2006.

My interest in neural development had sparked my interest in the fundamental principles of the organization of living systems, in particular the proper way to incorporate development, genetics and evolution within a unified theoretical framework. Tibor Ganti’s book “The Principles of Life” encouraged me to undertake the detailed modelling of protocell developmental dynamics and evolution. During my DPhil, I published conference papers on my basic model of template replication, simple models of the evolution of metabolism, and a journal paper on a formal model of dynamical hierarchies. However, my main achievement by far, possible due to the advice and guidance of Prof. Eors Szathmary, is a detailed stochastic model of nucleic acid dynamics, with proven predictive value for real chemical systems. We are currently preparing several publications based on results obtained using this model. The Marie Curie fellowship would allow me to extend our collaboration.

Additional Scientific Competences Arising from the Project

Having originally received a biological and clinical training, I undertook post-graduate study in computer science, becoming fluent in C, C++, Java, Perl, Mathematica and Matlab programming. I gained experience with a wide range of modelling techniques in artificial life, evolutionary computation, genetic algorithms and neural networks. However, I received no formal training in evolutionary theory or synthetic organic chemistry. Therefore, collaboration with Eors Szathmary is crucial if I am to constructively, i.e. without producing models that are of no use to anyone, apply my computational modelling skills to the field of pre-biotic chemistry. Work outside a computer science department, and in partnership with an eminent evolutionary biologist and chemist, would increase my competence. Due to the fruitful collaboration with Prof. Szathmary I have been introduced and collaborated closely with experts in stochastic modelling (Mons Ehrenberg and Johan Elf, Uppsala University) and in organic chemistry (Guenter Von Kiedrowski, Ruhr-University, Bochum).

Curriculum Vitae of Dr. Chrisantha Fernando

Date of Birth: 31-Oct.-1975

Place of Birth: Colombo, Sri-Lanka

Nationality: British.

Martial and family status: Married. No children.

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Positions

10/2005. – current	Postdoctoral Fellow, School of Computer Science, Birmingham, UK.
10/2004– 2/2005	Junior Research Fellow at Collegium Budapest, Institute for Advanced Study, Budapest, Hungary.
5/2001 – 8/2001.	Locum S.H.O Urology. Churchill Hospital. Oxford Health Care Trust.
5/2000-5/.2001	Junior House Officer. John Radcliffe Hospital, Headington, Oxford. Registered with the General Medical Council (UK)

2001.

Education

10/2002 – 12/2005	DPhil. in Computer Science. Centre for Computational Neuroscience and Robotics, Dept. of Biology/Dept of Computer Science. University of Sussex. Full EPSRC studentship.
2001-2002	M.Sc. in Evolutionary and Adaptive Systems. School of Cognitive and Computer Science (COGS), University of Sussex, UK.
1997-2000	B.M B.Ch. (Medicine) Wadham College, Oxford University, UK.
1994-1997	M.A. Physiological Sciences (1 st) Wadham College, Oxford University, U.K.
1992-1994	3 A-levels. Mathematics (A), Physics (A), Chemistry (A), St Brendan’s Sixth Form College, Bristol, U.K.
1987-1992	12 GCSEs, including astronomy. St Thomas More, Roman Catholic Secondary School, Bristol, UK.

Selected Publications with Abstracts

Chapters in Books

Szathmari, E, Santos, M, Fernando, C. (2005) *Evolutionary Potential and Requirements for Minimal Protocells*. Topics in Current Chemistry. 23rd August. Springer-Verlag Berlin Heidelberg. Vol 259: 167-211.

Articles in Journals

McGregor, S and Fernando, C. (2005) *Levels of Description: A Novel Approach to Dynamical Hierarchies*. Journal of Artificial Life, Special Issue on Dynamical Hierarchies. MIT Press. Vol 11(4): 459-472.

Fernando, C. Elf, J. Szathmari, E. (2006) *In Silico Experiments on the Origin of Long Nucleic Acid Template Replication*. (in preparation)

Papers in Conference Proceedings

Fernando, C. (2005) *The Good Symbiont*. Advances in Artificial Life: 8th European Conference, ECAL 2005, Canterbury, UK, September 5-9, 2005. Proceedings. 695-

Fernando, C and Di Paolo, E. A. (2004). *The Chemoton: A model for the origin of long RNA templates*. In Pollack, J., Bedau, M., Husbands, P., Ikegami, T. and Watson, R., editors, Artificial Life IX: Proceedings of the Ninth International Conference on the Simulation and Synthesis of Life, pages 1-8. MIT Press.

Fernando, C. and Sojakka, S. (2003). *Pattern recognition in a bucket*. In Banzhaf, W., Christaller, T., Dittrich, P., Kim, J.T. and Ziegler, J., editors, Advances in Artificial Life, Proceedings of the 7th European Conference on Artificial Life (ECAL 2003), pages 588-597. Springer. **(Winner of Best Paper Award)**

Presentations of Research at Conferences and Workshops.

Szathmary, E. Fernando, C. (2005) The replication problem. ESEB (European Society for Evolutionary Biology) 10th Congress.

Fernando, C. *Elongation vs. Replication of Nucleic Acids*. (2005) COST D27 Working Group Meeting for Prebiotic Chemistry. Evolution of Catalytic Networks of Chemical Species. Bled, Slovakia.

Fernando, C. *Stochastic Models of Non-Enzymatic Template Replication*. (2004) COST D27 Meeting for Prebiotic Chemistry, Hereklion, Crete.

Fernando, C. *CTRNN WORLD: A Model of Open-ended Evolution in a Dissipative System*. (2003) University of Hertfordshire Computer Science Technical Report 389 C. L. Nehaniv, P. J. Bentley & S. Kumar (Editors).

Fernando, C. *Parallel real-time computing with tap water*. (2003) EPSRC Cluster workshop. “Towards non-linear media computers”, Bristol. Organizer. A. Adamatsky.

MSc. Thesis work.

Fernando, C. A Situated and Embodied Model of Classical and Instrumental Conditioning. MSc Thesis (2003). CSRP, University of Sussex.

Fernando, C. Neural Mechanisms for Single-Episode Landmark Learning in Artificial Bees. (2002). CSRP, University of Sussex.

Popular Publications Arising

Duncan Graham-Rowe. Neural nets learn better with waves. 4th October 2003. **New-Scientist Magazine** Issue 2415. An article about our paper “Pattern Recognition in a Bucket.”

Teaching and Other Educational Activities

Expert presenter and neuroscience consultant for ‘The Human Mind’, a touring, interactive science show for BBC Education, (2004-2005).

Teaching graduate seminars in Artificial Life (Sussex University), Natural Computation (Birmingham University).

Principle organizer of the ‘*Units of life*’ reading group at Sussex that has been the venue for lectures by eminent speakers, such as the late John Maynard-Smith, Eors Szathmary, Joel Peck, and many others.

Principle organizer of the ‘*Computational Biology*’ lunchtime reading group at Birmingham university.

Other Research

Models of the mechanisms of autism.

In collaboration with Developmental Psychologists (Rachel Wood) and Philosophers of Mind (Hanneke De Jaegher) at the University of Sussex, I have developed models of a possible functional patho-physiology of autism due to a failure in an infant rhythm-based imitation system. By utilizing information from delays between ones actions and another person’s responses to ones actions, it is possible to infer whether the other person was expecting ones action. The capacity to detect these sub-response-time responses gives excellent evidence that the other agent was expecting ones action. No explicit reinforcement signals are required. Infants in which this system has failed may find it difficult to become socially fluid. I am currently developing a model of two coupled feed-forward controllers that attempt to learn each others behaviour.

Stochastic Models of the Evolution of Cell Signaling Networks.

I am currently employed at the School of Computer Science in Birmingham University in my first post-doc position working with Dr. Jon Rowe. My remit is to develop within a year, publications resulting from a stochastic model of the evolution of protein cell signalling networks that I have written. I have developed a genetic algorithm for simulating protein evolution by duplication and divergence, domain shuffling, and post-transcriptional splicing. The protein model itself is inspired by the work of Dennis Bray in Cambridge, with whom I have been in correspondence regarding the design of the models. I choose to describe a protein complex is a graph, proteins being the nodes. A protein node undergoes local-neighbourhood-dependent conformational changes, the local neighbourhood being the region of the graph separated by $< N$ branches from the protein node in question. The genome of each protein encodes the causes and effects of conformational change. Hopefully it will be possible to model the complex computations undertaken by large protein complexes, and to understand common evolutionary motifs in the evolution of computational strategies by protein networks.

Collaboration with Jarle Breivik (Oslo, Norway) on the Construction of Plastic Magnet Models of Template Replication.

I am collaborating with Dr. Jarle Breivik (<http://folk.uio.no/jbreivik/>), a cancer researcher at the University of Oslo, to design commercially viable self-replicating toys constructed from plastic magnets that simulate nucleic acid template replication ([US Patent 6,652,285](#))! I have arranged funding for visits by Dr Breivik and his post-doc students to Birmingham to meet with the nanotechnology department here, with the aim of developing mesoscopic physical models of protein signalling networks. Such physical models can be pedagogic as well as research tools.

ENDPAGE

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PART B Section 1

“PROPOSAL ACRONYM”

