8 Conclusions

This thesis revolves around the development of Evolutionary Algorithms (EAs) applied to optimization and model discovery in biological systems. Five independent topics of biological significance were addressed. Even though they are essentially unrelated, they share the sort of non-linear complexity that is typical of biological systems; and this makes them particularly well tailored for Evolutionary Algorithms, which are primarily computational methods designed for optimization of complex problems with large search spaces.

There is no optimal method for solving all types of optimization problems. An algorithm adequate for a certain class of problems may breakdown under a different problem. This became quite clear over the previous chapters; each problem had to be considered individually and a method to address it was developed. The framework followed for developing the algorithms in this work is usually applicable to any optimization problem that uses Evolutionary Algorithms:

1. *Nature of the problem* – to solve a problem it is necessary to understand it. This may sound like a tautology, but EAs need to be able to evaluate how good a solution is, if not in absolute terms, at least in relation to other candidate solutions. If a problem is well understood, a more reliable/realistic method to evaluate solutions can be developed.

2. *Modelling of the problem* – optimization is not carried out on the problem itself but on a model of the problem. This is an important distinction; a solution can be perfect for the model but, for the real problem, it is only as good as the model itself. Thus again the importance of understanding the nature of the problem. Knowledge of the problem allows the development of a model that captures and reflects its essential characteristics.

3. *Objective function* – arguably the most important component of EAs. The objective function is a measurement of how well a solution fits the model of the problem and is used to assign a fitness value to candidate solutions. In four of the problems considered in this work, the objective function and the fitness value were the same (direct 1:1 mapping); only in chapter 5 the objective function was used to assign fitness values based on the relative performance of solutions within the population (rank based selection).

4. *Development of an Evolutionary Algorithm* – depending on the problem a certain EA will be better suited than others. For example, it is now generally accepted that the original binary Genetic Algorithm is inefficient to solve real valued numerical problems. Alternative methods such as Differential Evolution are faster and yield better solutions. Two other important aspects are the design of efficient search operators and how to present the problem to an EA, ideally in a parameterisation that 'automatically' accommodates constraints (for example Kinghorn & Shepherd, 1999). Before summarizing the work of this thesis, one last question remains. Why use Evolutionary Algorithms? Essentially, they present various characteristics that are advantageous for solving optimization problems. Michalewicz & Fogel (2000:412-413) summarize these advantages as:

   1. Simplicity. The concept and the implementation of EAs are simple.

   2. Broad applicability. Virtually any problem can be addressed by EAs.

3. Hybrid methods. EAs allow integration with other methods.

4. Parallelism. The structure of EAs makes them particularly well suited for parallelization.

5. Robust to changes. Changes in the target system do not render the algorithm useless.

6. Self adaptation. The parameters of the EA can evolve alongside the solutions.

7. Solve problems with no known answers. Probably the greatest advantage of EAs; if an evaluation of goodness of fit of a solution is possible, EAs can be used.

The contributions of this thesis are summarized in the next sections. Emphasis is given to the Evolutionary Algorithms and software developed; contributions to the biological problems are also highlighted.

8.1 Nutrition Parameters in Beef Cattle

Beef cattle nutrition models (SCA 1990 and AFRC 1993, among others) can be used to predict economically important traits such as nutritional requirements, feed utilization and weight gain for a given set of parameters (quantity and ration formulation and cattle characteristics, for example). The problem is to find a set of parameters that maximizes the use of available resources to achieve target output(s). Differential Evolution (Price & Storn 1997), a simple and efficient heuristic for optimization of real valued problems, was implemented in the software LaGraZ. This software allows producers to predict daily live weight gain for a given diet as well as optimize ration formulations and daily allowances to meet specified nutritional targets. A good fit was obtained between experimental data of daily live weight gain from animal trials in comparison to those predicted by LaGraZ. The main advantage of the evolutionary approach – Differential Evolution – in relation to the commonly used Linear Programming is that the objective function is extrinsic to the optimization algorithm; which can be modified and/or additional targets can be included without significant changes to the heuristic. The entire nutrition model can be replaced without changes to the algorithm. The objective function was designed to accommodate simultaneous optimization of several targets (multicriteria optimization). Due to the flexibility of the Evolutionary Algorithm, it is straightforward to extend the objective function to include an additional target. For example, economic values – an important target for practical applications – can be included (the current version of LaGraZ is based solely on optimization of nutritional parameters).

8.2 Multiple Sequence Alignment

Multiple sequence alignment (MSA) plays an important role in molecular sequence analysis. An alignment is the arrangement of two (pairwise alignment) or more (multiple alignment) sequences of 'residues' (nucleotides or amino acids) that maximizes the similarities between them. Algorithmically, the problem consists of opening and extending gaps in the sequences to maximize an objective function (measurement of similarity). A simple Genetic Algorithm (GA) was developed and implemented in the program MSA-GA. GAs are well suited for this problem since residues and gaps are discrete units. An Evolutionary Algorithm cannot compete in terms of speed with progressive alignment methods but it has the advantage of being able to correct for initially misaligned sequences; which is not possible with the progressive method. This was shown using the BaliBase benchmark (Thompson et al. 1999b) where Clustal-W alignments were used to seed the initial population in MSA-GA, significantly improving them. Alignment scoring functions are an open field of research and it is important to have a tool that allows evaluation of new functions. The main contribution of this work was to develop a general evolutionary

framework for testing and implementing different scoring functions. Results have shown that a simple GA is capable of optimizing an alignment without the need of excessively complex operators used in prior work. The object oriented approach used in MSA-GA makes extending and/or replacing objective functions a trivial task.

8.3 Microarray Experimental Design

Spotted microarrays simultaneously provide information on thousands of genes. But they are costly and time consuming, which makes experimental design considerations an important topic. Experimental design is essentially an allocation problem of discrete, finite objects – select samples to hybridize on the same slide and assign dyes to the samples. A Genetic Algorithm was developed to optimize the experimental design of spotted microarrays using a weighted multicriteria objective function. The method was implemented in ArrayDesigner which can be used to search for optimal/near-optimal designs for a given set of user-defined parameters. Optimal designs are known for studies that use a small number of samples and slides (Kerr & Churchill 2001); for these the GA evolved comparable designs. The advantage of the GA is that it can be used to optimize large designs with many samples and slides, which is computationally intractable by exhaustive search. To our knowledge this is the first time a GA has been used for microarray experimental design optimization.

8.4 S-Systems Modelling of Genetic and Biochemical Networks

Modelling of biological processes has become an important research topic to understand processes from a systems point of view. Driven by the ever-growing availability of data – with gene expression data a major source – genetic and biochemical models try to explain how the components and their interactions affect the behaviour of the entire system. The most common approach to modelling is through differential equations; which include S-Systems (Voit 2000). Method and code to convert directed graphs of networks into S-Systems equations was developed and implemented in SimArray. Even though the method is generic, the *theme* of the program is microarrays; it also includes basic stability and sensitivity analyses, plots and data of simulations, and generates simulated microarray datasets. A major difficulty with S-Systems is identifying an appropriate set of parameter values for a model. Differential Evolution (Price & Storn 1997) is used to optimize model parameters (rate constants and kinetic orders). Results with time course simulated data of fermentation in *Saccharomyces cerevisae* show that a full parameter set evolved that fits well four out of five of the time-course data points and adequately models the dynamics of the system. This is the first work that provides a simple method for constructing S-Systems (automatically converts graphs into equations) and uses an EA for estimation of parameter values.

8.5 Reconstruction of Genetic and Biochemical Pathways

The ultimate modelling method will allow construction of entire models, fully parameterized from biological datasets. This goal is still out of reach, but some steps can be taken to advance the research. A hybrid EA was developed to evolve models of biological processes as systems of differential equations and simultaneously co-evolve a set of parameters for these models from time-series data. Gene Expression Programming (Ferreira 2001), a Genetic Programming variant was used for model inference with an embedded Differential Evolution (Price & Storn 1997) for model parameterization. A simple

method for reducing bloat in Gene Expression Programming was also developed. To test the algorithm, a computational tool with several heuristic methods for construction of systems of equations (functions $f(x)$ or differential equations dx/dt) from user defined datasets was developed. Simulated data from two mathematical models of the *lac operon* was used to compare the hybrid method with Gene Expression Programming; it was shown that the hybrid method is significantly superior. For model parameterization, Differential Evolution was superior in comparison to other heuristic methods. This justifies its use in the other real valued numerical optimization problems of this thesis. There is a great potential for EAs in reconstruction of pathways; the hybrid algorithm is a step in the right direction.

8.6 Final Remarks

All biological topics studied in this thesis are actively being researched; new discoveries are constantly being made and have to be incorporated into the optimization tools. Here lies the main advantage of Evolutionary Computation over other methods: the ease with which new information – new objective functions – can be adopted without changes to the heuristic. Over the previous chapters it became clear that for most of the topics alternative objective functions are available or better ones are necessary. As new functions are developed they can immediately replace old ones, if an evolutionary framework is employed. This flexibility also makes EAs a useful tool for comparing different objective functions under a common framework. Regardless of discussions on whether the objective functions used in this work are superior to others, all the algorithms and code developed can easily be modified to target a different function. Computationally, the programs are object oriented and a new objective function is a simple matter of replacing a single class. All software is freely available from the author.

The five biological topics discussed are complex and of practical importance. For each an Evolutionary Algorithm was developed and implemented in a fully functional *ready to use* program. The methods and their corresponding programs were evaluated as to their optimization capabilities. The results show that Evolutionary Algorithms are efficient for addressing complex biological problems. Many biological questions are being studied using EAs; and with the ever increasing volume of biological data, it can be expected that the use of EAs will only keep on growing. Evolutionary Computation has come full circle; originally inspired by biological processes, it has found its way back into biology to help investigate complex, challenging and relevant problems.

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