Welcome to BioGEC Tutorial!

Biological Applications of Genetic and Evolutionary Computing

GECCO 2004

Wolfgang Banzhaf / James Foster
Memorial University / University of Idaho

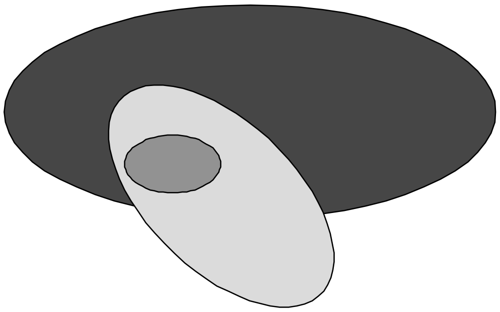
History of this tutorial

- Who we are
  - James A. Foster. Professor Computer Science, Biological Sciences, Philosophy, and Bioinformatics & Computational Biology (director) at U. Idaho; also U. Washington Med. School and Idaho State U. Director of Idaho Bioinformatics Core.
  - Wolfgang Banzhaf. Professor and Chair, Computer Science, Memorial University, Newfoundland. Editor in Chief, Genetic Programming & Evolvable Hardware.
- BioGEC workshops: GECCO 2002, 2003, 2004
- GPEM special issue: Out or coming soon
- BioGEC track at GECCO ‘04

Our motivation

- Build dialogue between GEC and Biological Science
  - GEC researchers answering biologically relevant questions
  - Biological Scientists answering GEC questions
- "Repay the debt" to Biological Sciences

What's the Problem?



□ What we want to know
□ What we can handle
□ What we know
(not to scale)

Biology:	Polymers	In space	Interact	It's Alive!
Data:	Sequences	Structures	Graphs	Simulations

Examples of Questions

- Are there other molecules like mine?
- How do my molecules make my organism function?
- How do my molecules (or organisms) interact with others?
- Where did my molecules (or organisms) come from?

Outline

- Overview of Biology as relevant to our context (JF)
- What is GEC good for? (WB)
- Q & A session (all)
- 4 Applications in depth
  - Sequence Alignment (JF)
  - Gene Expression (WB)
  - Phylogenetic Inference (JF)
  - Networks (WB)
- Summary, open problems, discussion (all)

What‘s missing

- Protein structure, protein folding, etc.
- Ecology
- Neuroscience and other modeling
- Much much more…alas

PART I

(Really) Basic Biology

James A. Foster

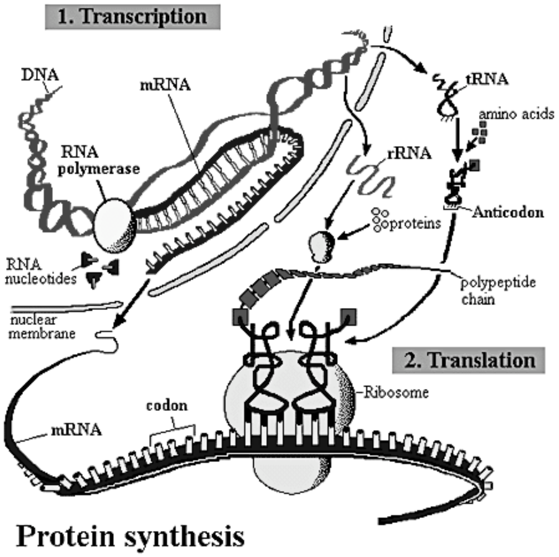
Overview

***Biology*: How living things do what they do, and how they came to do it.**

Similar to languages, we need to understand

- *Sequences*, like nouns
- *Structure*, like grammar
- *Function*, like structure
- *Ecology*, like a text
- *Evolution*, like linguistics

From DNA to Proteins



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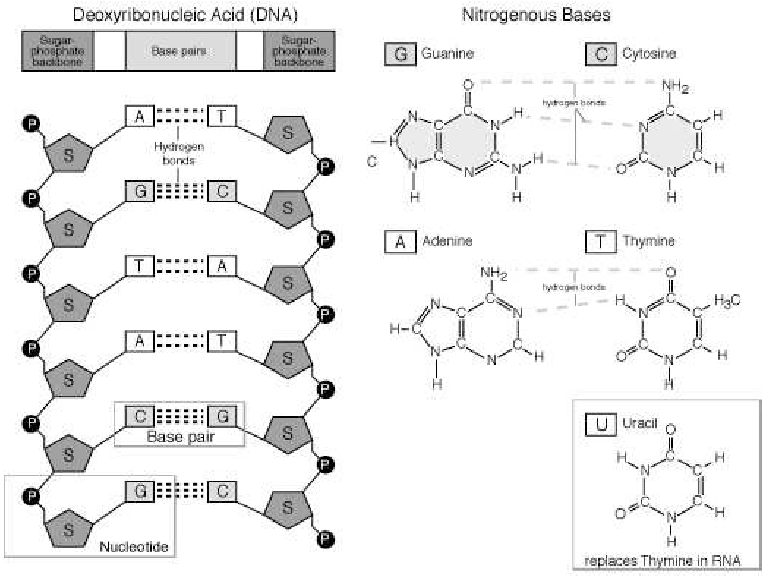
DNA: Illustration



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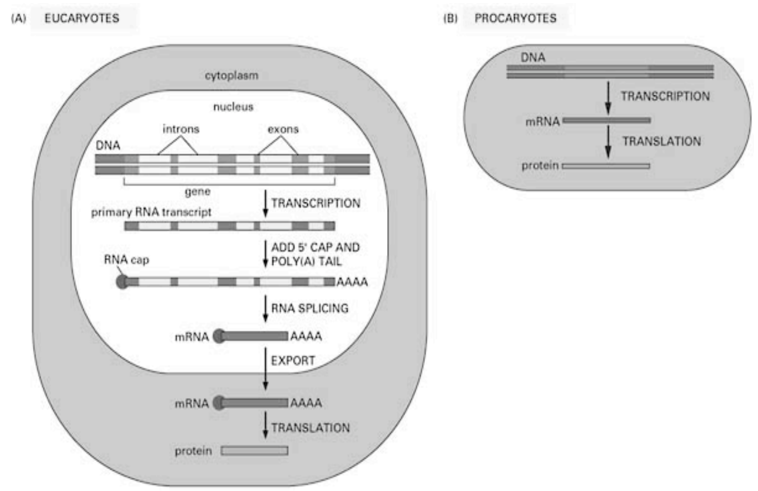
Steps during translation



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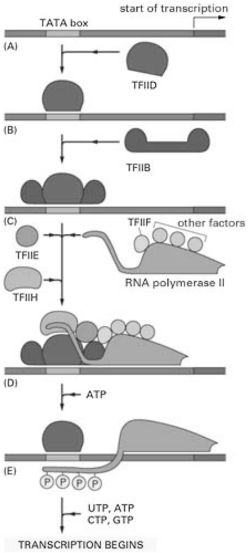
Transcription: starting & editing



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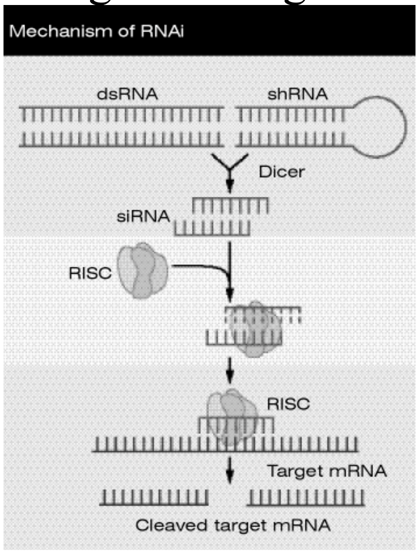


DNA to RNA

- Enzymes (e.g. relaxase) unwind DNA
- Enzymes (e.g. rna synthetase) makes complementary pre-mRNA (A→U, C→G, G → C, T → A)
- Enzymes edit pre-mRNA to get mRNA: removing introns, rearranging exons, correcting errors, etc.

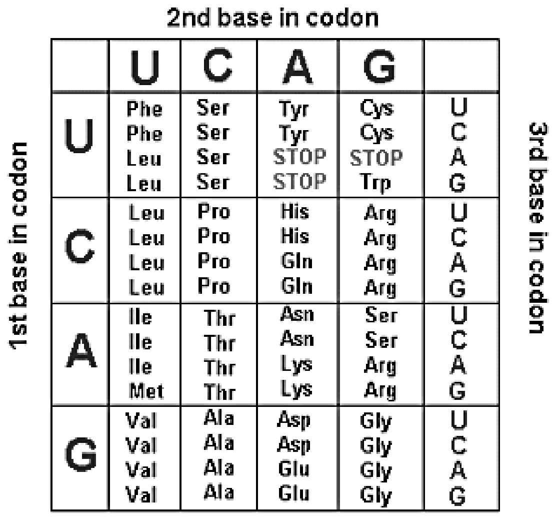
Proteins

- Backbone
- Side chain of amino acids (aka residues)
  - 20 available
  - Different chemical properties
- Structures: alpha coils, beta sheets
- Where the action is: interact with other molecules (DNA, RNA, proteins)

RNA to proteins

- Ribosome (a protein) binds to RNA at start codon (usually AUG)
- Reads 3-nucleotide *codon* in appropriate *Open Reading Frame (ORF)*
- Binds to *tRNA*, which is linked to *amino acid* (determined by *genetic code*)
- Transfers tRNA residue to growing protein
- Moves to next codon
- Detaches at stop codon (UAA, UAG, or UGA)

The genetic code



2nd base in codon

1st base in codon	U	C	A	G	3rd base in codon
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

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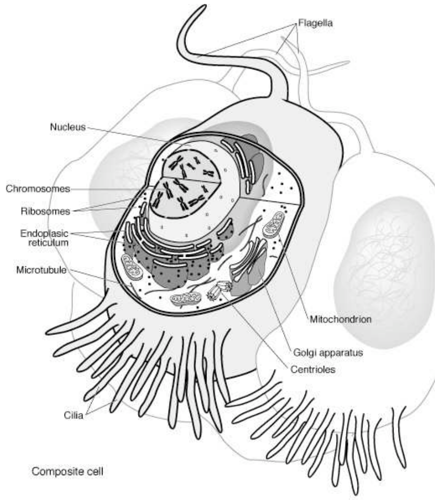
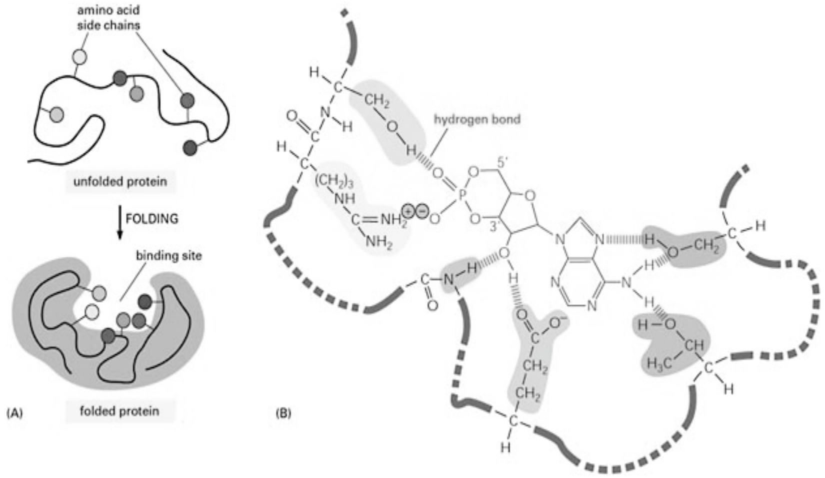
Cells: where it all happens

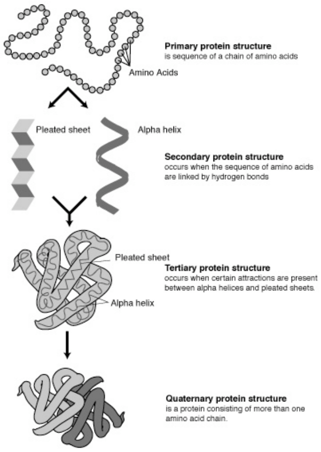


How proteins work



Structure

Proteins


Primary protein structure
is sequence of a chain of amino acids
Amino Acids
Pleated sheet
Alpha helix
Secondary protein structure
occurs when the sequence of amino acids are linked by hydrogen bonds
Pleated sheet
Tertiary protein structure
occurs when certain attractions are present between alpha helices and pleated sheets.
Alpha helix
Quaternary protein structure
is a protein consisting of more than one amino acid chain.

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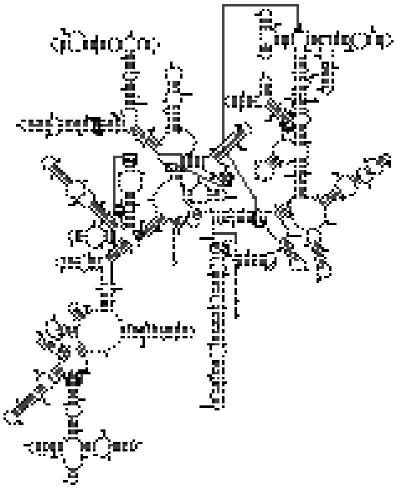
Nucleic Acids



Proteins to Life

The new protein

- Folds as determined by *chemystery*
- Is transported to appropriate place (in, on, or outside of cell membrane or equivalent)
- Binds to its target
- Changes conformation
- And the magic continues…

Types of DNA

- Genomic
  - Genic: codes for proteins for the host (30K in humans, 100K proteins)
  - Non-Genic (95% of humans)
    - RNA coding
    - Regulatory
    - Mobile elements (over 40% of humans)
    - Endogenous retroviruses
- Non-genomic
  - Organelles (mitochondria, chloroplasts)
  - Plasmids

Evolution

- Errors happen:
  - While transcribing: misreads, slipping, breaks, exon duplication, gene duplication
  - While sitting in the cell: rearrangements, chromosomal duplication
  - From the outside: viruses, mobile elements
- Isolated populations get different errors
- We observe only those differences that persist
  - Because they actually help (selection)
  - Or just because (neutral evolution)

“Ecology”

Studies distribution, abundance, interactions of organisms & environment

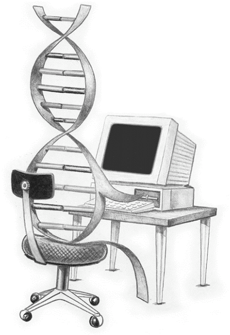
- Why are organisms distributed the way they are (modeling)?
- How does speciation happen (evolution)?
- Define & quantify inter-species interactions (systems science/networks)?
- What is role of randomness in biological systems (modeling)?

Part II
What is GEC good for?

Wolfgang Banzhaf

What is GEC good for?

- What is GEC ?



www.genetic-programming.org

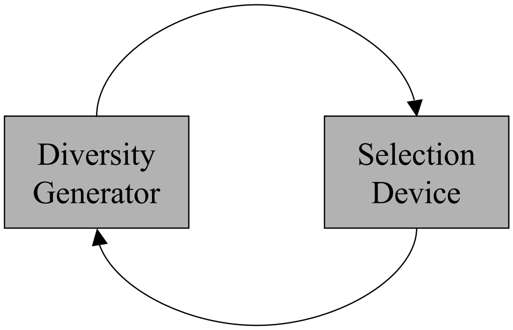
Mr. Darwin in the Computer

What is Genetic and Evolutionary Computing?

A Darwinian approach to computing:

The variation – selection loop

- Invalidates probability argument
- Appreciates relative performance advantages



Our problems with complex problems

- The intellectual and a VCR remote control
- Lost in high-dimensional spaces

What is Genetic and Evolutionary Computing? (II)

- A population of “solutions” is subjected to the GEC algorithm
- Solutions consist of elements which can be combined and of parameters which need to be determined
- The GEC-algorithm uses
  - Operators for reproduction, mutation and recombination (for the production of new solution variants)
  - An evaluation measure (fitness)
  - A selection operator

What is GEC good for? (II)

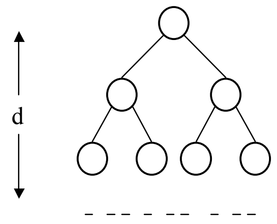
- High-dimensional search spaces
- Ill-posed problems
  - You know what you want, but not how to achieve it
- Noise and variation
- Non-parametric search
  - Rugged search landscapes, discrete structures
- Non-linear model building

Key GEC results

- High-dimensional search spaces: Treatable
- Ill-posed problems: Approachable
- Noise and variation: Not harmful
- Non-parametric search: Possible
- Non-linear model building: Possible

Large Search Spaces are treatable

- Typical GA search space ≈ 10^{100}
- Typical GP search space ≈ 10^{100000}



F={AND, OR, NOR, NAND}

T={x_1, x_2, x_3}

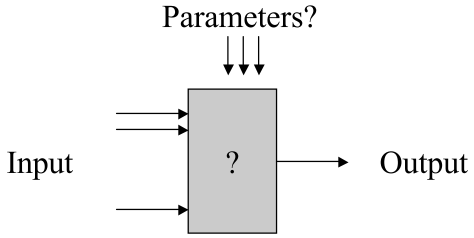
N(6) ≈ 10^{69}

N(17) ≈ 10^{143735}

Ill-posed problems

Subset of Inverse problems: Given a collection of observed data and a model generation mechanism / a model and parameters to choose:

•Find the best model / model parameters to fit the data



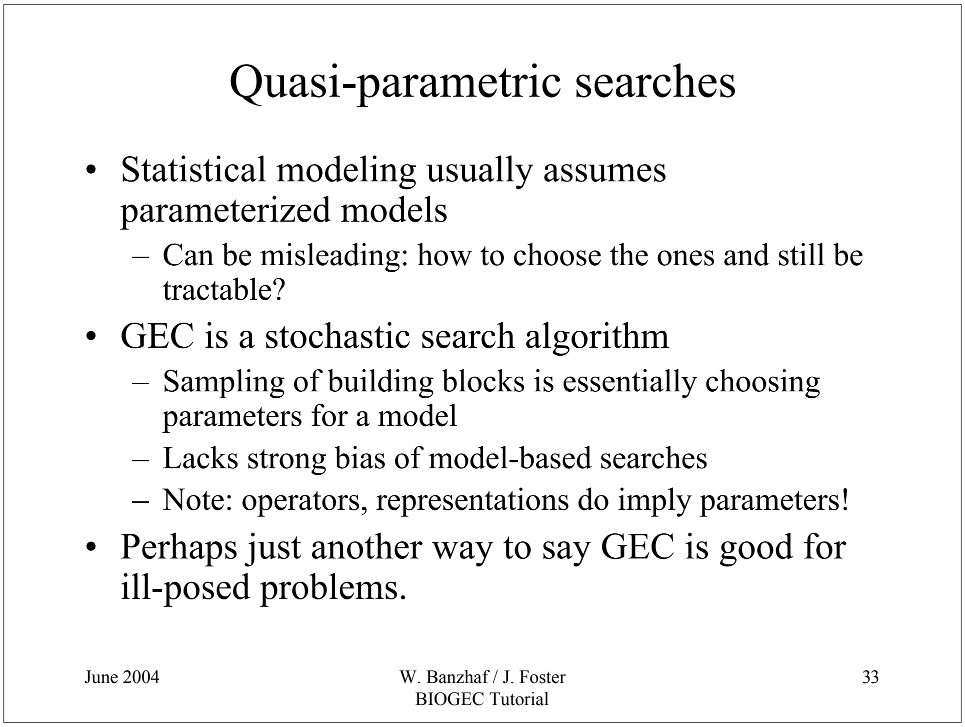
Parameters?

Input

?

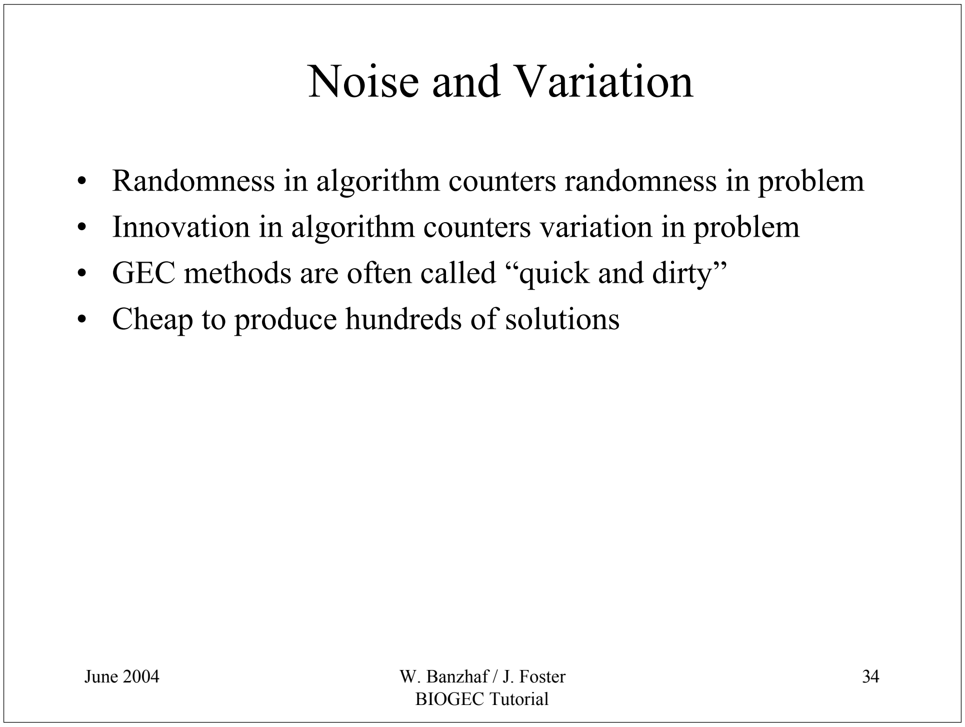
Output

Ill-posed: A problem is well-posed when a solution *exists*, is *unique*, and *depends continuously on the initial data*. It is *ill-posed* when if fails to satisfy *at least one* of these criteria. (Hadamard)



Quasi-parametric searches

- Statistical modeling usually assumes parameterized models
  - Can be misleading: how to choose the ones and still be tractable?
- GEC is a stochastic search algorithm
  - Sampling of building blocks is essentially choosing parameters for a model
  - Lacks strong bias of model-based searches
  - Note: operators, representations do imply parameters!
- Perhaps just another way to say GEC is good for ill-posed problems.



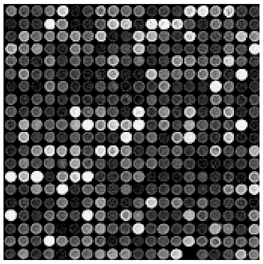
Noise and Variation

- Randomness in algorithm counters randomness in problem
- Innovation in algorithm counters variation in problem
- GEC methods are often called “quick and dirty”
- Cheap to produce hundreds of solutions

Summary and Outlook

Problems in Biology often are:

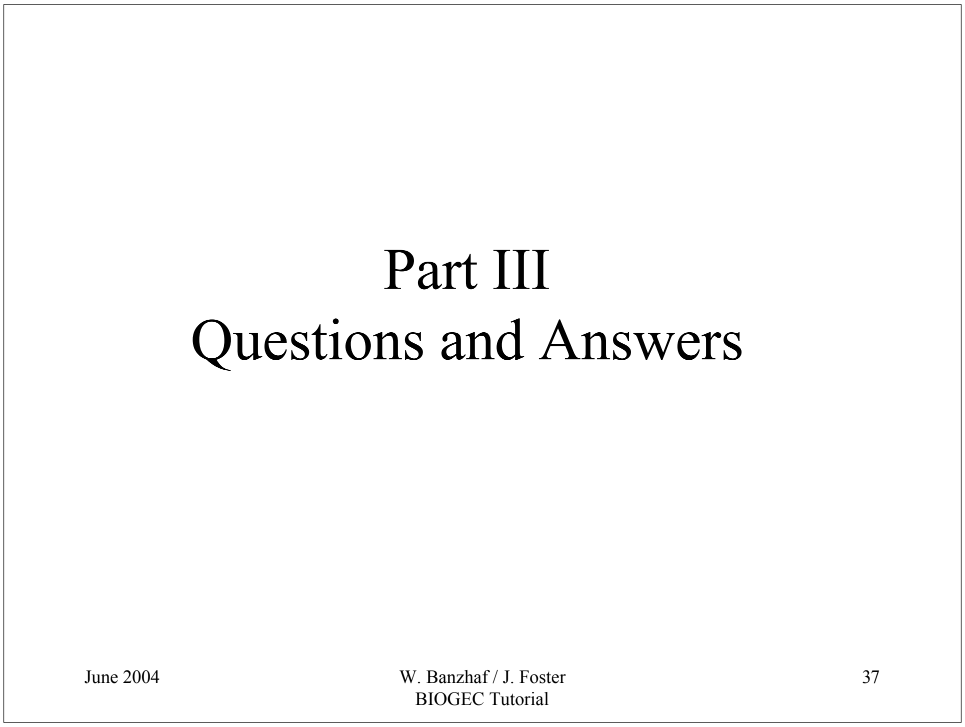
- High-dimensional
- Ill-posed
- Noisy
- Non-parametric
- Non-linear



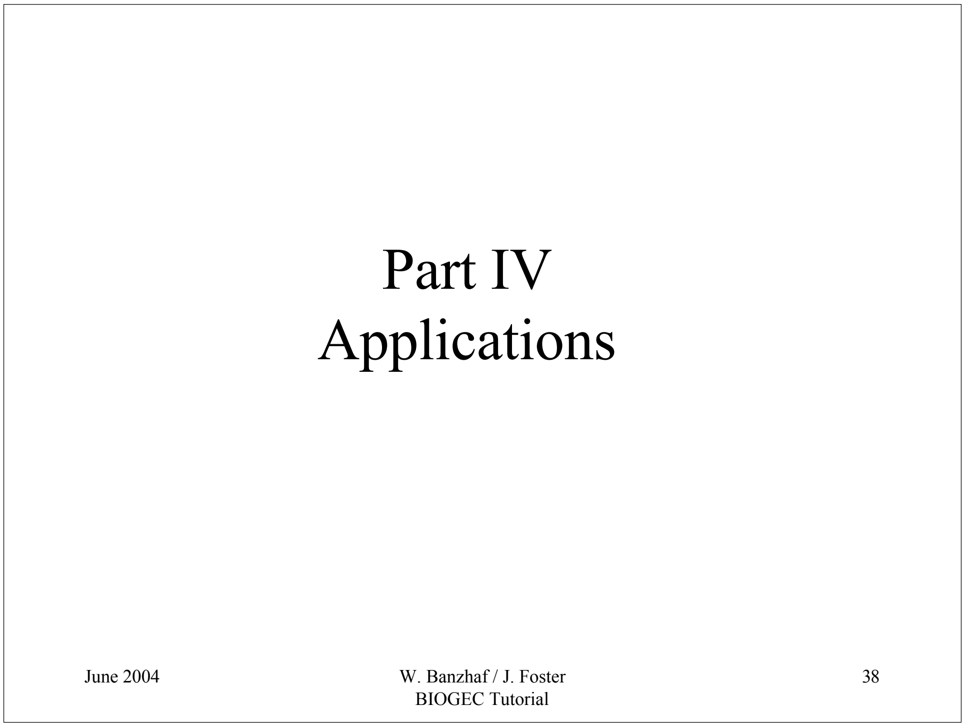
As we move into understanding biological systems, i.e. move from descriptive to explicative models, we need powerful techniques such as GEC

Challenges

- Can we get rid of Evolution after we have learned about what it does?
- NP-hardness isn‘t enough of a justification
- When not to use EC?



Part III
Questions and Answers



Part IV
Applications

Multiple sequence alignment

James A. Foster

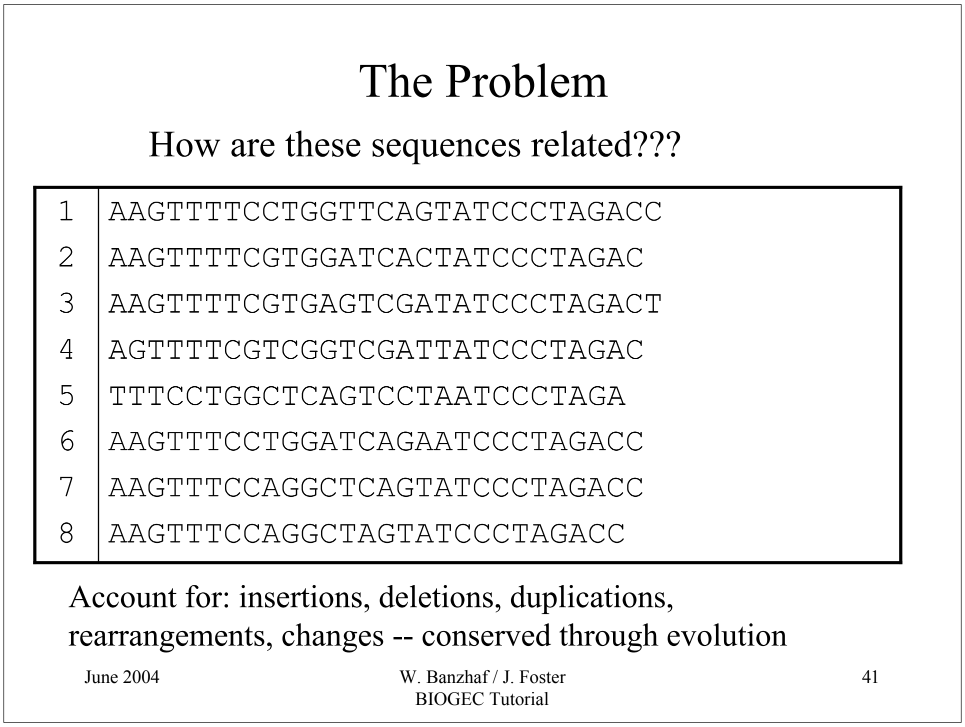
What is the problem?

***Informally*: line up sequences so that the columns show observed state of homologous residues**

Used to detect related regions of sequence, for further analysis

Given: n sequences (taxa) & scoring system

Find: assignment of characters to columns such that columns optimize the score

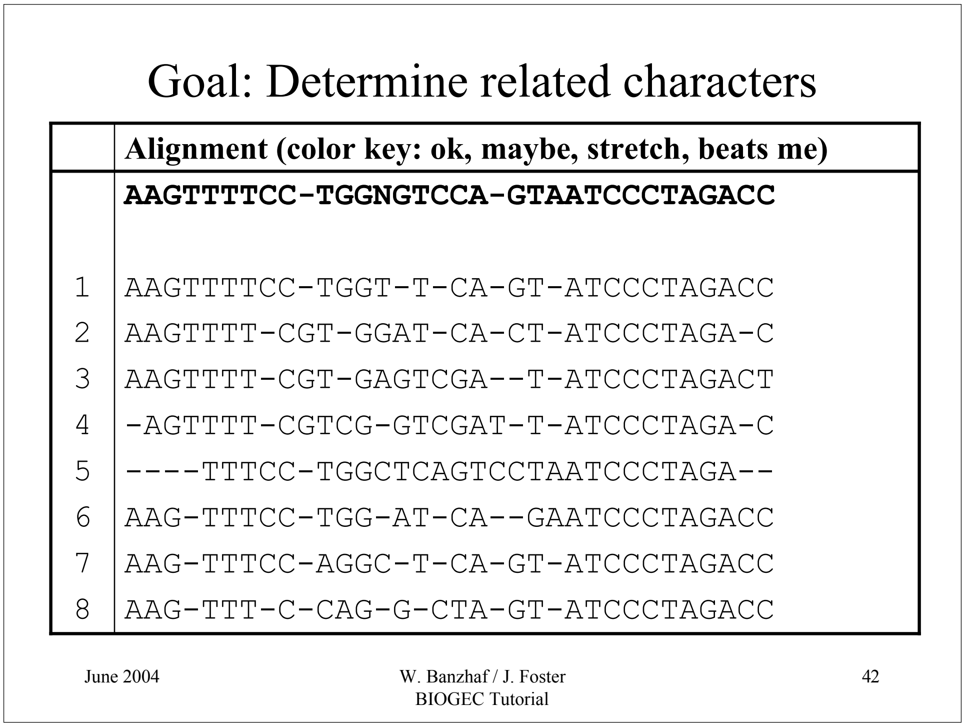


The Problem

How are these sequences related???

1	AAGTTTTCCTGGTTCAGTATCCCTAGACC
2	AAGTTTTCGTGGATCACTATCCCTAGAC
3	AAGTTTTCGTGAGTCGATATCCCTAGACT
4	AGTTTTCGTCGGTCGATTATCCCTAGAC
5	TTTCCTGGCTCAGTCCTAATCCCTAGA
6	AAGTTTCCTGGATCAGAATCCCTAGACC
7	AAGTTTCCAGGCTCAGTATCCCTAGACC
8	AAGTTTCCAGGCTAGTATCCCTAGACC

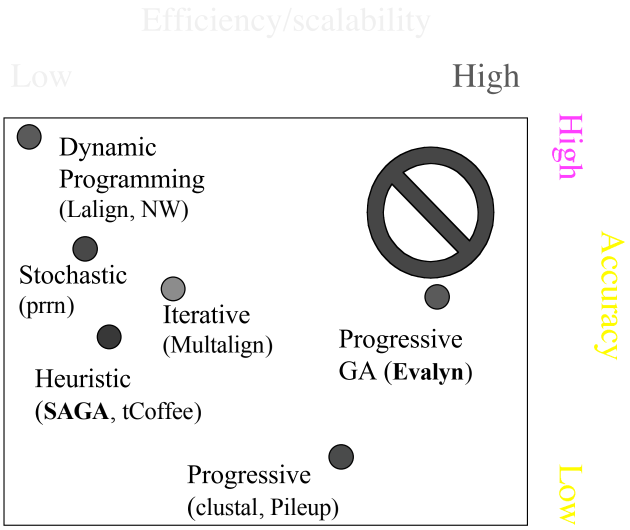
Account for: insertions, deletions, duplications, rearrangements, changes -- conserved through evolution



Goal: Determine related characters

	Alignment (color key: ok, maybe, stretch, beats me)
	AAGTTTTCC-TGGNGTCCA-GTAATCCCTAGACC
1	AAGTTTTCC-TGGT-T-CA-GT-ATCCCTAGACC
2	AAGTTTT-CGT-GGAT-CA-CT-ATCCCTAGA-C
3	AAGTTTT-CGT-GAGTCGA--T-ATCCCTAGACT
4	-AGTTTT-CGTCG-GTCGAT-T-ATCCCTAGA-C
5	----TTTCC-TGGCTCAGTCCTAATCCCTAGA--
6	AAG-TTTCC-TGG-AT-CA--GAATCCCTAGACC
7	AAG-TTTCC-AGGC-T-CA-GT-ATCCCTAGACC
8	AAG-TTT-C-CAG-G-CTA-GT-ATCCCTAGACC

(Global) MSA Algorithms



Efficiency/scalability

Low

High

High

Accuracy

Low

Dynamic Programming (Lalign, NW)

Stochastic (prrn)

Iterative (Multalign)

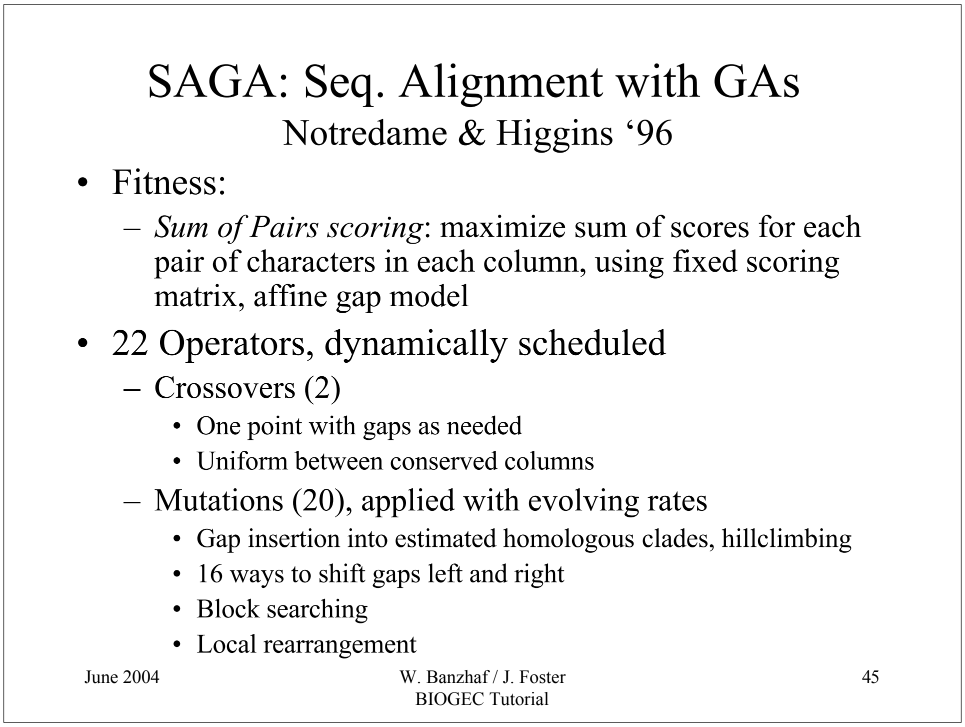
Heuristic (**SAGA**, tCoffee)

Progressive GA (**Evalyn**)

Progressive (clustal, Pileup)

GEC approaches

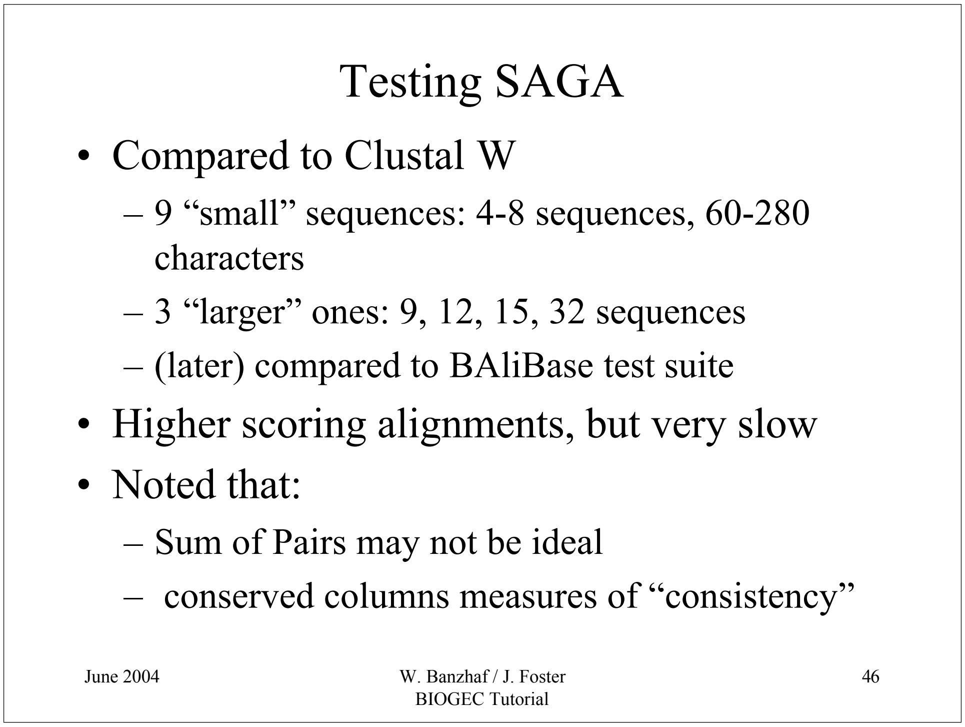
- Placement of gaps
  - Directly (Zhang & Wong; Chellapilla & Fogel; Shyu et al.)
  - With heuristic rules (Notredame (SAGA))
- Evolving guide trees (Sheneman et al. (Evalyn))



SAGA: Seq. Alignment with GAs

Notredame & Higgins ‘96

- Fitness:
  - *Sum of Pairs scoring*: maximize sum of scores for each pair of characters in each column, using fixed scoring matrix, affine gap model
- 22 Operators, dynamically scheduled
  - Crossovers (2)
    - One point with gaps as needed
    - Uniform between conserved columns
  - Mutations (20), applied with evolving rates
    - Gap insertion into estimated homologous clades, hillclimbing
    - 16 ways to shift gaps left and right
    - Block searching
    - Local rearrangement



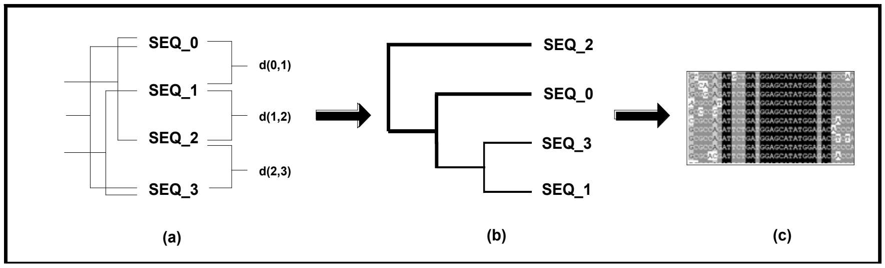
Testing SAGA

- Compared to Clustal W
  - 9 “small” sequences: 4-8 sequences, 60-280 characters
  - 3 “larger” ones: 9, 12, 15, 32 sequences
  - (later) compared to BAliBase test suite
- Higher scoring alignments, but very slow
- Noted that:
  - Sum of Pairs may not be ideal
  - conserved columns measures of “consistency”

Progressive MSA (e.g. Clustal)

Build a *guide tree* (b) (neighbor joining or UPGMA) from pairwise distances (a)

Align pairs of sequences from bottom up, using dynamic programming (c)

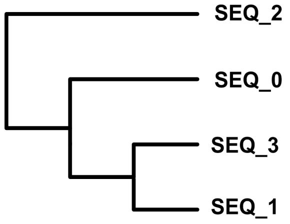


EVALYN: EC for progressive MSA

Idea: discover better guide trees by combining “good” features through evolution

Result: superior alignments (measured by sum of pairs scoring), faster algorithm for large numbers of taxa

Evolve this!



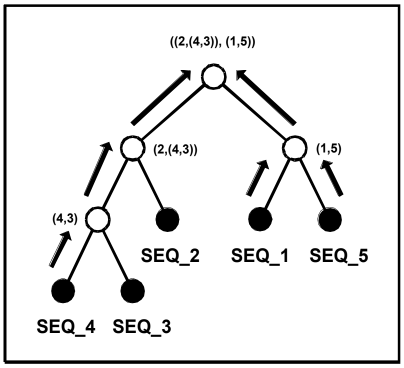
Initialization & Representation

- *Initial population*: randomly generated rooted, bifurcating trees, with each taxon labeling exactly one leaf
- *Representation of individuals*: bifurcating trees with each taxon uniquely present in leaves

Fitness

Build alignment progressively using individual guide tree

- *Sum of pairs*: for each column, add score for aligning each pair of characters; add column scores



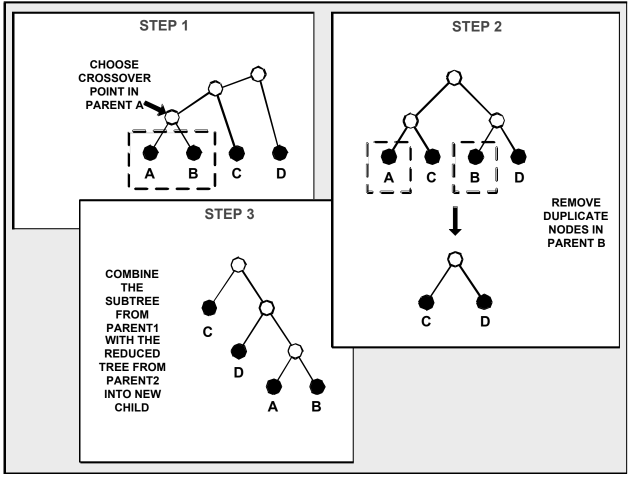
Progressively Aligning Sequences Using a Guide Tree

Selection & Replacement

- Each individual (genotype) produces an alignment (phenotype) with a score (fitness)
- Individuals selected for reproduction with recombination & mutation proportionally to fitness
- Children replace individuals (guide trees) with lower fitness

Recombination

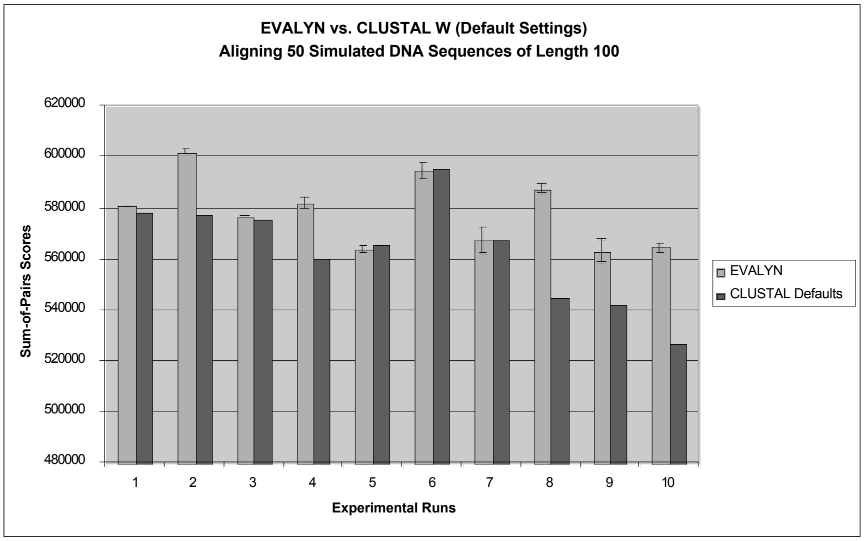
- Branch swapping *between* two trees


STEP 1
CHOOSE CROSSOVER POINT IN PARENT A
A
B
C
D
STEP 2
A
C
B
D
REMOVE DUPLICATE NODES IN PARENT B
C
D
STEP 3
COMBINE THE SUBTREE FROM PARENT1 WITH THE REDUCED TREE FROM PARENT2 INTO NEW CHILD
C
D
A
B

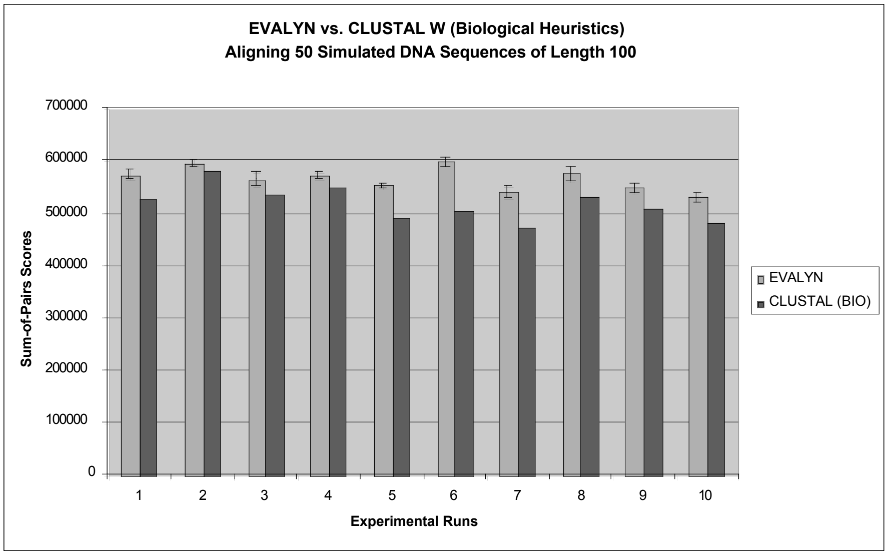
Experimental Setup 1

- Simulate 50 DNA sequences of 100 bp under Jukes-Cantor model
- Align with EVALYN and CLUSTAL (default/adaptive, biological, basic parameters)
- Use CLUSTAL to score alignments
- EVALYN Parameters:
  - Population Size = 500
  - Iterations = 25,000
  - Mutation Rate = 0.01
  - Match = 2.0, Mismatch = 0.0, Gap Open = -10, Gap Extend = -.1

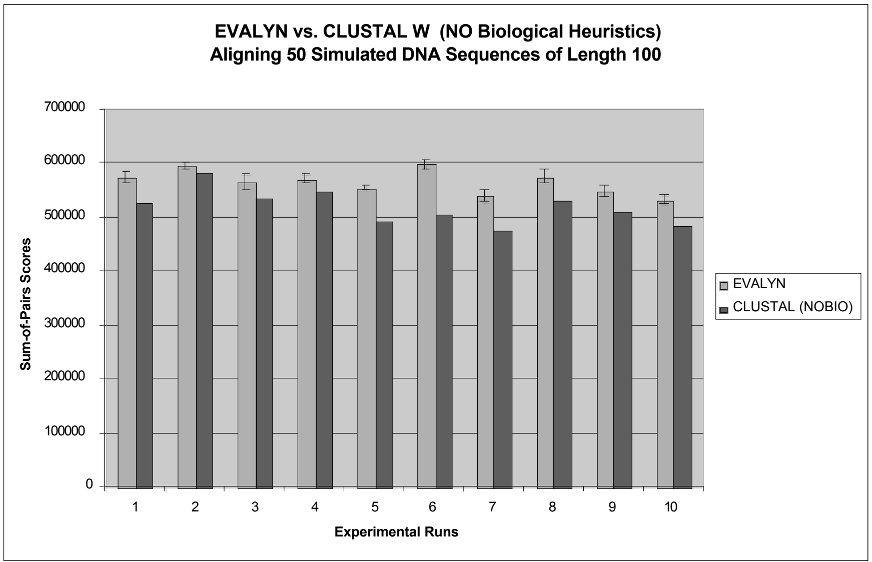
Results: DNA simulation, defaults

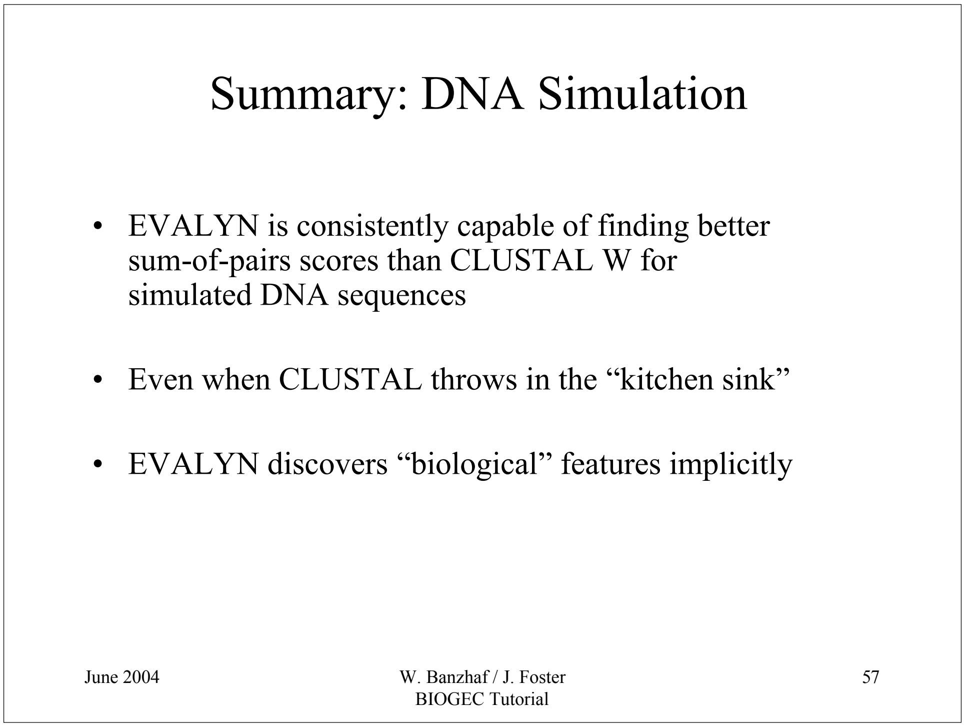


Results: DNA Simulations, biological



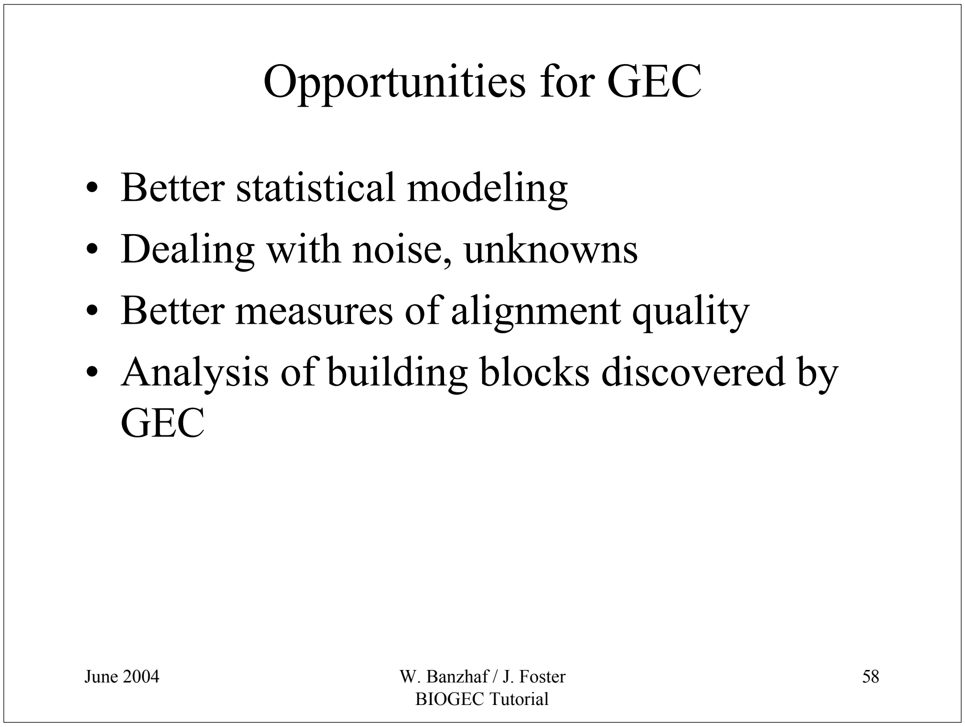
Results: DNA Simulations, basic





Summary: DNA Simulation

- EVALYN is consistently capable of finding better sum-of-pairs scores than CLUSTAL W for simulated DNA sequences
- Even when CLUSTAL throws in the “kitchen sink”
- EVALYN discovers “biological” features implicitly



Opportunities for GEC

- Better statistical modeling
- Dealing with noise, unknowns
- Better measures of alignment quality
- Analysis of building blocks discovered by GEC

Gene Expression

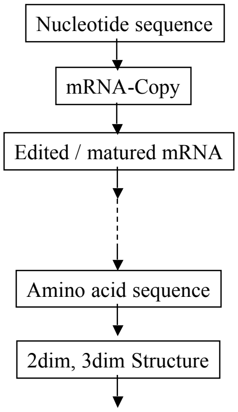
Wolfgang Banzhaf

Outline

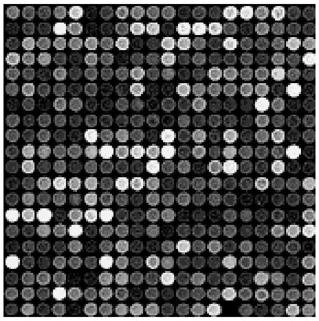
- What is the problem?
- What methods exist to solve it?
- What has been done with GEC?
- A specific approach
- Opportunities for GEC

What is the problem?

- Life is dynamic - DNA looks inert
- There needs to be a translation between the two
- Central dogma



Gene Expression Data



Fluorescence data regarding preferential hybridization of expressed genes (RNA)

•Experimential noise (cross-hybridization, optical problems,…)
•Relative rather than absolute signals (background, etc)
•Different scanners, different chip manufacturers
• Artifacts from preparation of the cells (temperature dependence, concentrations of solvents, etc)
•Time-dependence of expression
•Large number of signals (features)

How can we discern patterns, e.g. of healthy vs. cancerous tissue?
Which are the genes that have most influence on the decision?

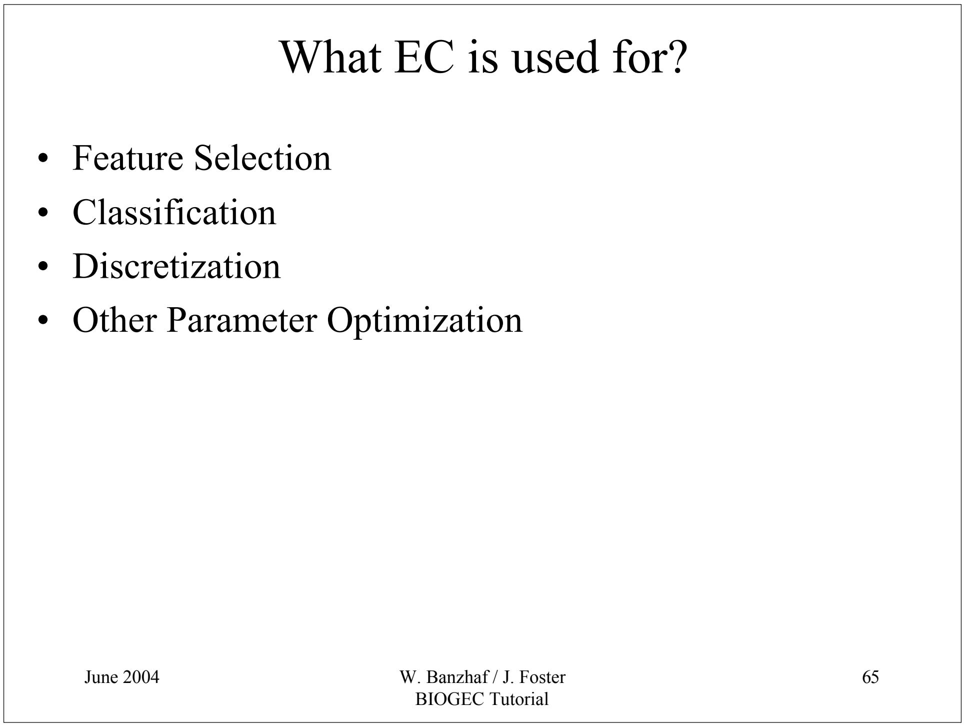
Aktivität in Reaktionen Verhalten Aktivität von I/O pairs

What is the problem? (II)

- Noise
- Experimental variation
- Abundance of features vs. small number of patterns (relative)
- High-dimensionality (absolute)

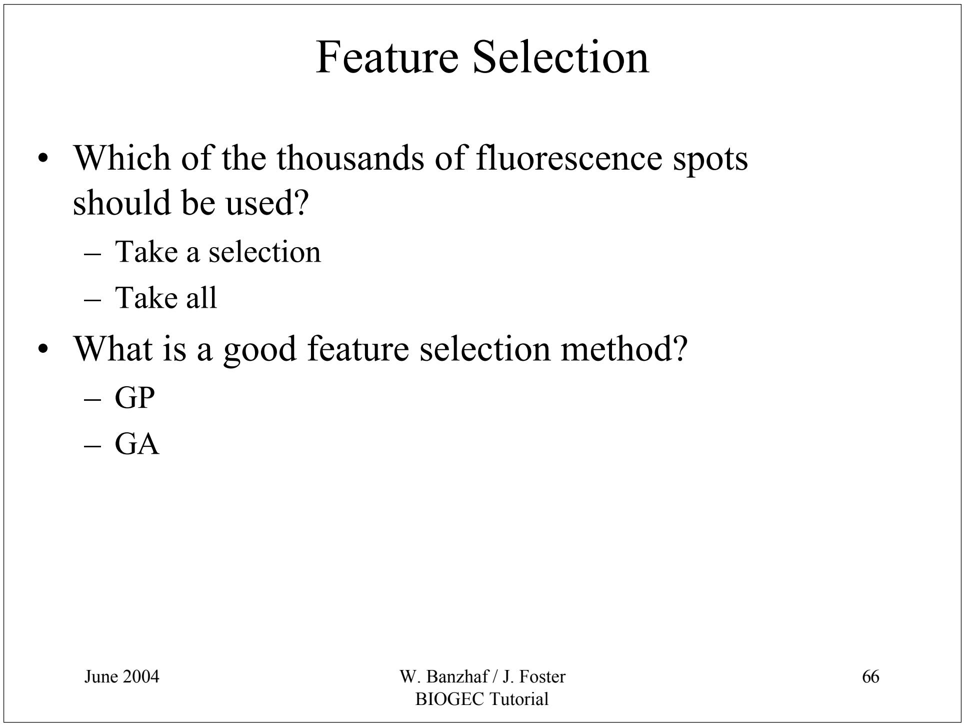
What methods exist to solve it?

- Nearest neighbor
- Support vector machine
- Other machine learning approaches
- Self-organizing maps
- Other neuro and fuzzy approaches
- Evolutionary Computation



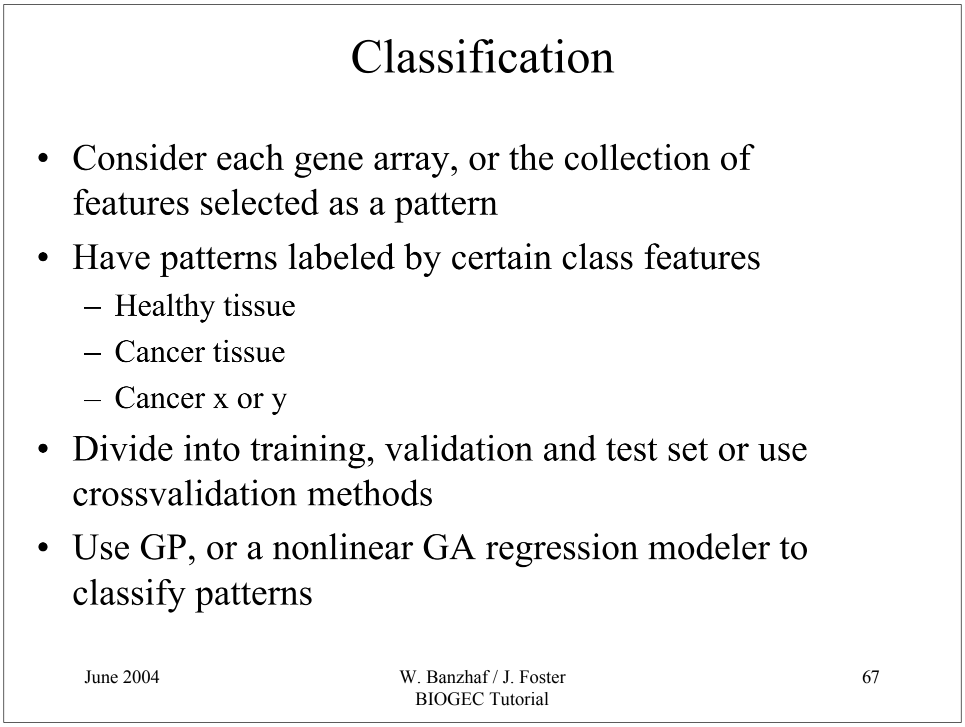
What EC is used for?

- Feature Selection
- Classification
- Discretization
- Other Parameter Optimization



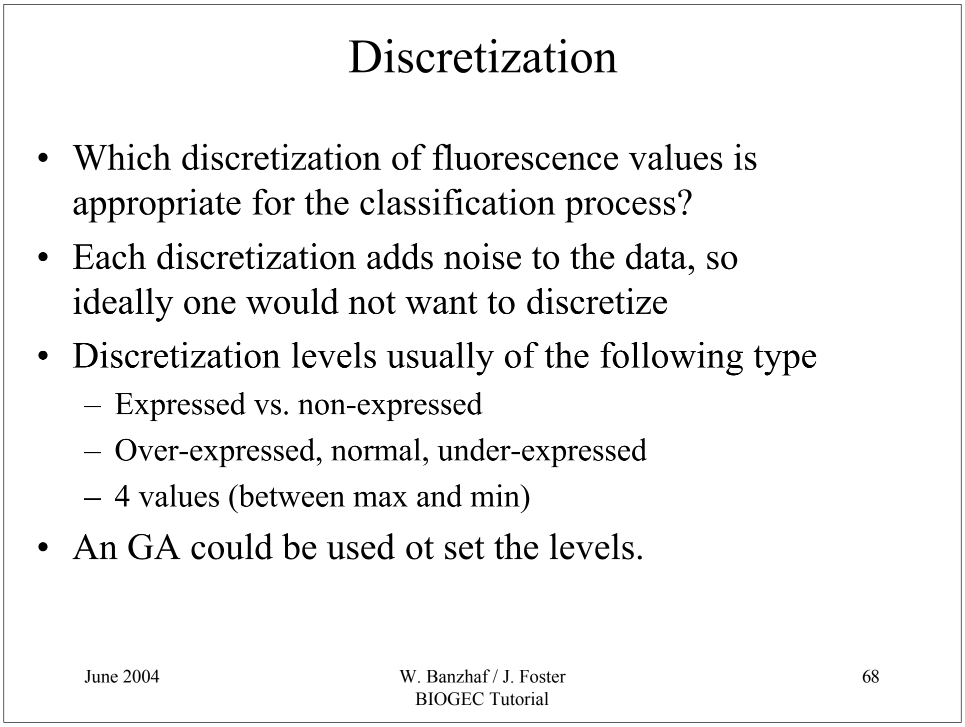
Feature Selection

- Which of the thousands of fluorescence spots should be used?
  - Take a selection
  - Take all
- What is a good feature selection method?
  - GP
  - GA



Classification

- Consider each gene array, or the collection of features selected as a pattern
- Have patterns labeled by certain class features
  - Healthy tissue
  - Cancer tissue
  - Cancer x or y
- Divide into training, validation and test set or use crossvalidation methods
- Use GP, or a nonlinear GA regression modeler to classify patterns



Discretization

- Which discretization of fluorescence values is appropriate for the classification process?
- Each discretization adds noise to the data, so ideally one would not want to discretize
- Discretization levels usually of the following type
  - Expressed vs. non-expressed
  - Over-expressed, normal, under-expressed
  - 4 values (between max and min)
- An GA could be used ot set the levels.

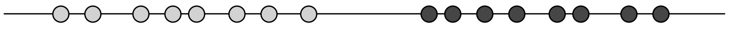
What we do

- Random selection
- Standard deviation $\mathrm{rel}_{\mathrm{S.d.}}(x) = \sqrt{\sum_{i=1}^{n} \frac{1}{n}(x_i - \mu)^2}$
- Partitioning into two classes $\mathrm{rel}_{\mathrm{p}}(x) = \frac{\mu_{>\mu} - \mu_{\leq\mu}}{\sigma_{>\mu} + \sigma_{\leq\mu}}$
- Difference of average values $\mathrm{rel}_{\mathrm{Av.difference}}(x) = | \mu_0 - \mu_1 |$
- Signal-to-Noise ratio $\mathrm{rel}_{\mathrm{SNR}}(x) = \frac{| \mu_0 - \mu_1 |}{\sigma_0 + \sigma_1}$
- Number of clusters

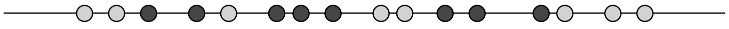
Number of Clusters

Difference of number of components and number of 0/1- resp. 1/0- transitions.

„Valuable Gene“:



„Worthless Gene“:

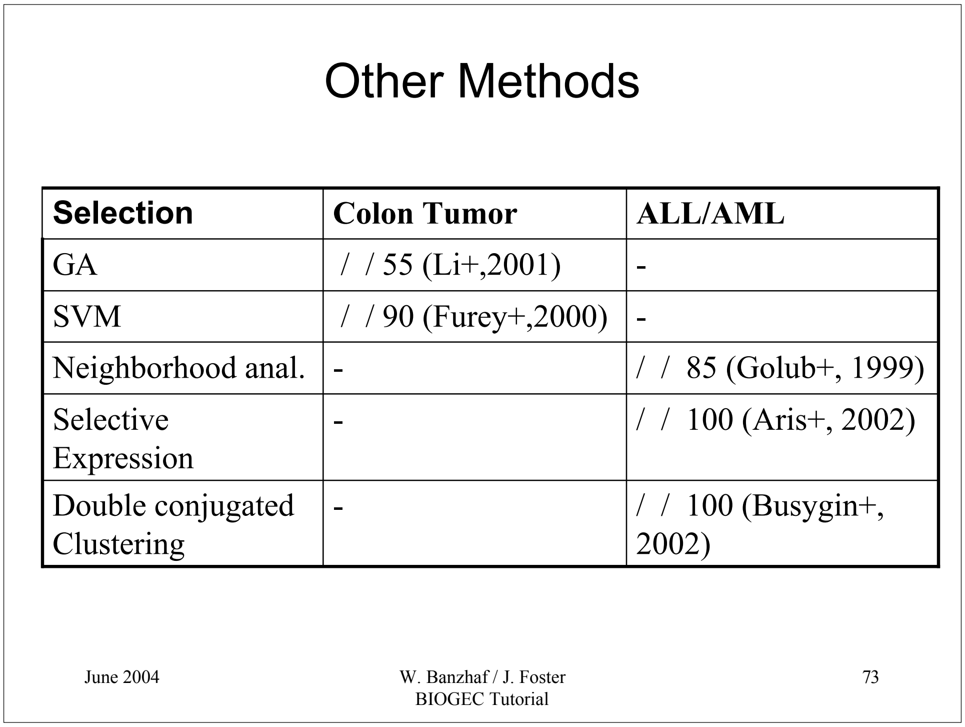


GP-runs with Discipulus

- Binary Classification
- 3 subsets: Training, Validation, Applied
- Standard parameters
- 100 runs per experiment
- Different numbers of features

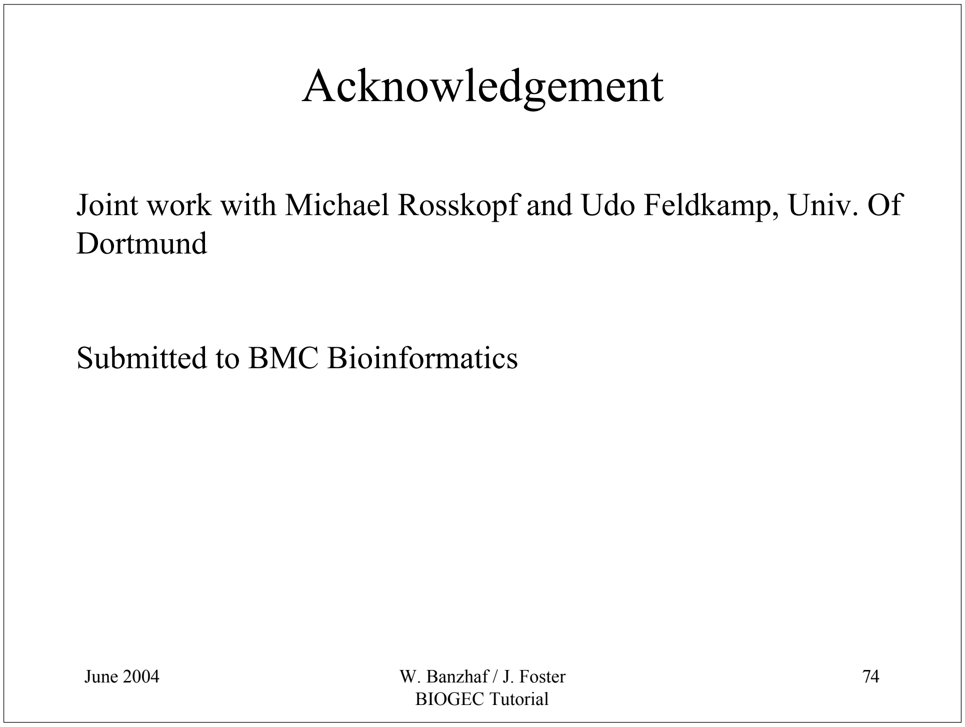
Results (10 Features)

Selection	**Colon Tumor**	**ALL/AML**
Standard Deviation	100 / 86 / 75	100 / 75 / 67
Two Partition	**100 / 90 / 95**	**100 / 100 / 100**
Mean Difference	100 / 90 / 75	100 / 96 / 96
Signal-to-Noise	100 / 100 / 80	100 / 100 / 96
Cluster Count	100 / 95 / 80	100 / 100 / 96
Random (Mean values)	96 / 90 / 71	97 / 85 / 72



Other Methods

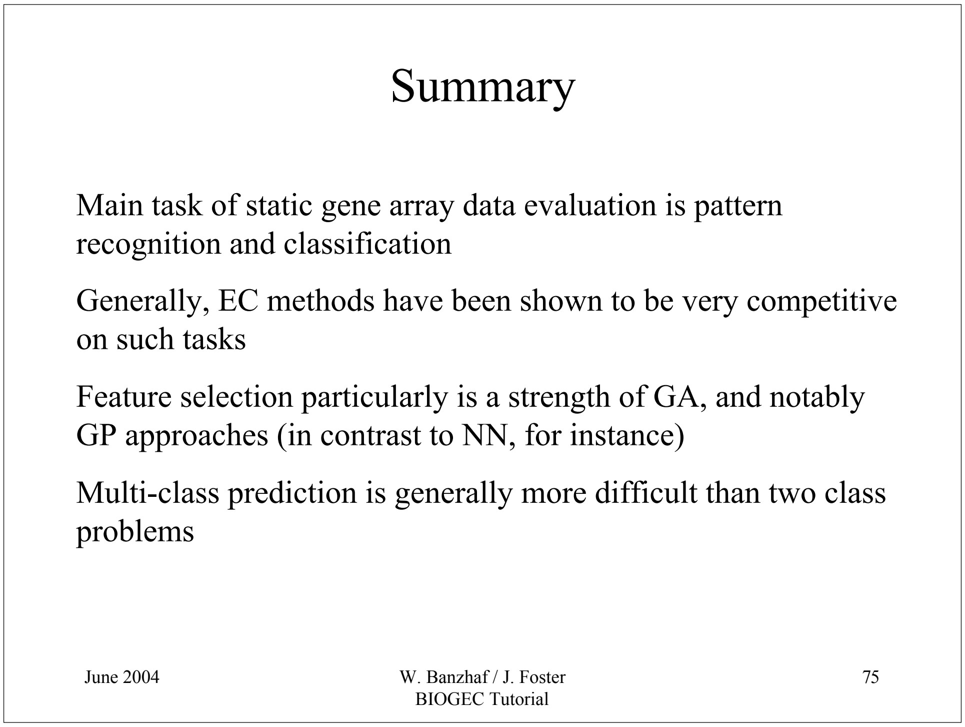
Selection	Colon Tumor	ALL/AML
GA	/ / 55 (Li+,2001)	-
SVM	/ / 90 (Furey+,2000)	-
Neighborhood anal.	-	/ / 85 (Golub+, 1999)
Selective Expression	-	/ / 100 (Aris+, 2002)
Double conjugated Clustering	-	/ / 100 (Busygin+, 2002)



Acknowledgement

Joint work with Michael Rosskopf and Udo Feldkamp, Univ. Of Dortmund

Submitted to BMC Bioinformatics



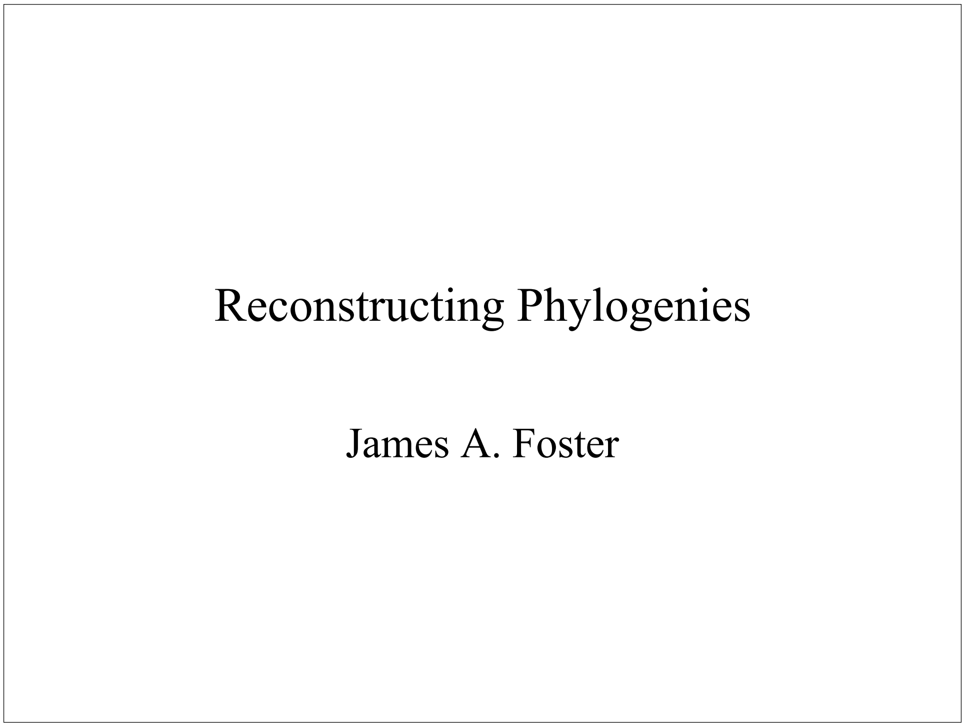
Summary

Main task of static gene array data evaluation is pattern recognition and classification

Generally, EC methods have been shown to be very competitive on such tasks

Feature selection particularly is a strength of GA, and notably GP approaches (in contrast to NN, for instance)

Multi-class prediction is generally more difficult than two class problems



Reconstructing Phylogenies

James A. Foster

The Problem

- Given: characters related by evolution
- Find: correct (or plausible) evolutionary history that produced them

- Applications:
  - Finding related genes or gene products
  - Resolving taxonomies

- Challenges
  - Vast search spaces
  - Parameter rich statistical modeling

Current Approaches

- Distance based algorithms
  - Maximum parsimony: minimize changes required to explain data
  - Clustering: group sequences by similarity
- Model based algorithms
  - Maximum likelihood: find tree that maximizes probability of data, given model of evolution

GRAPHYL (Congdon-Bates)

- Find tree that minimizes number of changes along branches (maximizes parsimony)
  - Representation: canonical form determined by input dataset
  - Fitness: parsimony of trees
  - Crossover:
    - Select subtree in parent 1
    - Select smallest subtree in parent 2 with same leaves
    - Exchange, prune duplicate leaves
  - Mutation: swap randomly selected leaves
  - Island model GA with migration

Testing GRAPHYL

- Compare to Wagner parsimony utility in Phylip
  - on two datasets of binary characters: 23 species, 29 characters of Laminaflorii; 49 species, 61 attributes of angiosperm data
- GRAPHYL found comparable trees
  - Found many identical trees

GAML (Lewis)

Find tree that maximizes (log)likelihood of data

- Representation: Tree with branch lengths, transition/transversion ratio (evolution model); Island model in 2002
- Fitness: ln(probability of data|T)
- Mutation
  - Random (with Gamma distribution) change in branch lengths
  - Random subtree pruning & Regrafting
  - Alter transition/transversion ratio
- Crossover
  - Randomly select subtree in parent 1
  - Remove sequences in that subtree from Parent 2, simplify
  - Graft first subtree into Parent 2 at random point

Testing GAML

- 55 taxa cloroplast problem (in 1998)
- 5000 character, 228 taxa simulated; 4822 character, 228 taxa rRNA (2002)

- Found high likelihood trees, but not best known
- Possible antagonism between objectives: finding topologies & branch lengths

Opportunities for GEC

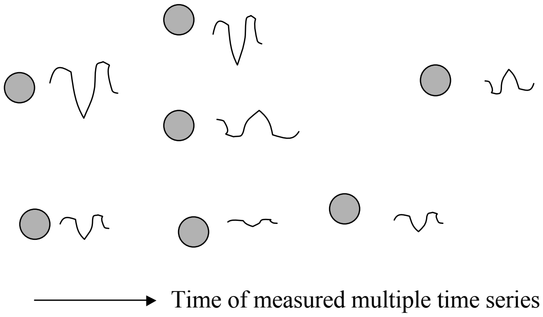
- Multiple trees
- Model selection
- GEC for importance sampling
- Reticulate evolution

Gene Networks

Wolfgang Banzhaf

What is the problem?

Gene network reconstruction from gene array time series data



What is the problem? (II)

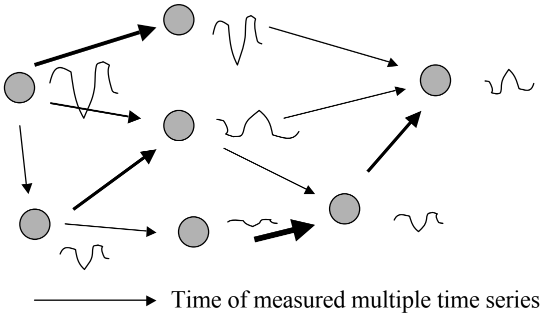
- Noise
- Experimential variation
- Time dependence of data
- Very small number of time sampling points
- High costs of running experiments
- Observed genes trivially correlated?

Preparation

- Knock-out experiments
- Strong perturbations of the network
- Different initial conditions / unnormal values of certain genes

The goal

Goal of network reconstruction: Determine the links between genes



The more data the more restrictions for links, the more unique the solution

What methods exist to solve it?

- Boolean networks (binary values)
- Discrete networks a la R. Thomas
- Weight Matrices
- Bayesian Networks (no cycles)
- Dynamic Bayesian Networks
- Differential equations (small numbers of genes)
- Difference Equations
- EC techniques

- Researchers generally prefer statistical methods due to the noise inherent in the experimental techniques
- Large number of possibilities: 20 genes -> 10^72 DAGs

What has been done with GEC?

- Parameter optimization for differential equation coefficients
- Bayesian Networks (node ordering)
- Belief Network coefficients
- Boolean Network coefficients
- Time series prediction using GA/ES/GP

A specific approach

Ando/Iba: Construction of a Genetic Network using an Evolutionary Algorithm and Combined Fitness Function (Genome Informatics 14, 2003, pp.94-103)

Parameter Estimation of a S-system network model: Excitatory and inhibitory (nonlinear) regulation of genes. Parameters are $(\alpha_i, \beta_i, g_{ij}, h_{ij})$

$$\frac{dx_i}{dt} = \alpha_i \prod_{j=1}^{N} x_j^{g_{ij}} - \prod_{j=1}^{N} x_j^{h_{ij}}$$

Noise model between true expression $S(x_k)$ and measured/assumed expression x_k is Gaussian with std.dev constant over time and equal over all genes

$$\varepsilon_k = N(x_k - S(x_k), \sigma)$$

Fitness function to minimize: AIC=log-likelihood of a model + # degrees of freedom

$$\Lambda(M, \sigma) = -\frac{1}{2\sigma^2} \sum_{t=1}^{T} [x(t) - S(x(t)]^2 - \frac{T}{2} \ln(2\pi\sigma^2)$$

A specific approach II

2 phase GA: (1) Estimation of parameters for each gene and its regulators $(\alpha_i, \beta_i, g_{ij}, h_{ij})$
(2) Estimation of parameters of the whole network

Tests with artificial data (networks artificially generated + noise added)

E.Coli data: Tryptophan metabolism (PNAS 97 (2000) 12170-12175
3 time series, 5 time points each (starvation and overdose of tryptophan)

Results: Artificial networks well reconstructed, simple natural system with problems due to noise levels.

Opportunities for GEC

- General ODE models for gene expression (eg by GP)
- Devise good fitness functions
- Learn to deal with noise levels
- Study artificial models of regulatory networks (what is optimized by a regulatory network?)
- Include prior knowledge into modeling tool
- Suggest a set of models instead of just one

Summary, Open Problems, Discussion

What do you think???

Further information

References for Case Studies

This is NOT a complete bibliography, it only lists work discussed directly in this tutorial

Multiple Sequence Alignment

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Books

- **Bioinformatics: The Machine Learning Approach**, P.Baldi and S. Brunak.
- **Introduction to Computational Biology: Maps, Sequences and Genomes**, M.S. Waterman.
- **Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids**, R. Durbin, S. Eddy, A. Krough and G. Mitchinson.
- **Algorithms on Strings, Trees and Sequences: Computer Science and Computational Biology**, D. Gusfield.

- **Evolutionary Computation in Bioinformatics**, G.B. Fogel, D.W. Corne (eds.).
- **Foundations of Systems Biology,** H. Kitano (ed.)
- **Computational Modeling of Genetic and Biochemical Networks,** J. Bower and H. Bolouri (eds.)

Journals

- Bioinformatics
- J. Computational Biology
- J. Bioinformatics & Comp. Biology
- Briefings in Bioinformatics

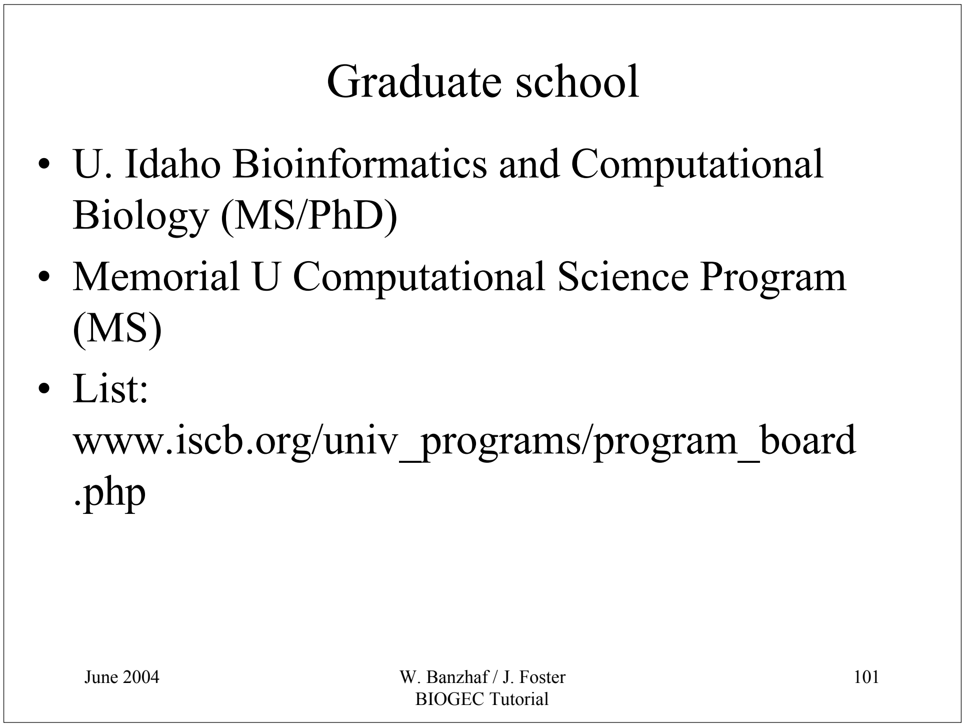
- Nucleic Acids Research
- J. Systematics
- J. Molecular Evolution
- Proc. Nat. Academy of Sciences

Webpages

- Int. Soc. For Comp. Bio: www.iscb.org
- Tutorials: www.techfak.uni-bielefeld.de/bcd/original-welcome.html
- NIH/NCBI: www.ncbi.nlm.nih.gov/Education/index.html
- Bioplanet: www.bioplanet.com/links.htm

Conferences

- Pacific Symposium on Biocomputing (PSB)
- Research in Computational Biology (Recomb)
- Intelligent Systems in Molecular Biology (ISMB)
- Genetic & Evolutionary Computation Conference (GECCO)
- Congress on Evolutionary Computation (CEC)
- Evolution meetings: evolution04.biology.colostate.edu



Graduate school

- U. Idaho Bioinformatics and Computational Biology (MS/PhD)
- Memorial U Computational Science Program (MS)
- List: www.iscb.org/univ_programs/program_board .php