Application of local search methods in cost-effectiveness analysis: the case of rheumatoid arthritis

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Background

- Rheumatoid Arthritis – chronic condition treatable by disease-modifying anti-rheumatic drugs (DMARDs)
- DMARDs singly or in combination
- This work considers sequential use of single DMARDs

Underlying Model

- Birmingham Rheumatoid Arthritis Model (BRAM)
- Individual sampling model (stochastic simulation) generates sequence of virtual patient histories
- Mean costs and quality adjusted life years for strategy under various assumptions

Comparing Two Strategies

- Single run of model can compare two strategies
- Difference discounted to divergence point
- No absolute measure of the value of a strategy
- Gives better choice of two strategies at stated threshold incremental cost-effectiveness ratio

Strategy Space

- When this work started, 11 DMARDs – approximately 40 million possible orders
- Allow subsequences – over 100 million strategies
- Cannot test all of them
- Now 14 DMARDs – 237 billion strategies
- For *n* drugs, trunc(*e.n*!) strategies

Descent Algorithm

- Start with random sequence
- Compare with limited set of other sequences (“neighbours” of starting sequence)
- Run for enough patients until *z* score for net monetary benefit is at least 4
- Continue until current sequence better than all its neighbours

Base Case Result 1

- Infl – AZA – DPen – SSZ – Ana – LEF – CyA – MTX – GST – Etan – HCQ

1. Infl – AZA – DPen – SSZ – Ana – LEF – CyA – MTX – GST – HCQ – Etan
2. Infl – AZA – DPen – SSZ – Ana – LEF – CyA – MTX – GST – HCQ
3. Infl – AZA – DPen – SSZ – Ana – LEF – MTX – CyA – GST – HCQ

Base Case Result 2

- After 35 changes, process terminates at
- SSZ – MTX – HCQ – LEF – GST – DPen – CyA – AZA
- Rerun from new starting sequence
- Etan – Ana – Infl – AZA – CyA – DPen – GST – LEF – HCQ – MTX – SSZ
- After 55 changes, same finishing point

Interpretation of Results

- Not sensible to say that one of 100 million strategies is right and all others are wrong
- Implication would be that all non-optimal strategies are equally bad
- Rather, final sequence reached is sensible basis for discussion between clinician and patient

Genetic Algorithm

- Random starting “population” of strategies
- Form next generation of strategies from two “parent” strategies
- Mutation to ensure coverage of whole decision space
- Replace some or all of current generation by new strategies
- Must favour better strategies at some point

Random Starting Set

Pall	SSZ	CyA	LEF	Etan	AZA	DPen	Ana	GST	MTX	HCQ	Infl
CyA	HCQ	MTX	Pall	GST	SSZ	Etan	DPen	LEF	AZA	Ana	Infl
AZA	SSZ	HCQ	Ana	Infl	Pall	DPen	Etan	MTX	GST	CyA	LEF
LEF	GST	CyA	Ana	Infl	MTX	HCQ	AZA	Pall	Etan	DPen	SSZ
CyA	Etan	Ana	Pall	HCQ	AZA	GST	DPen	LEF	MTX	SSZ	Infl
HCQ	SSZ	Etan	Pall	LEF	Infl	CyA	AZA	DPen	Ana	GST	MTX
CyA	MTX	HCQ	GST	LEF	Ana	Etan	DPen	Pall	AZA	SSZ	Infl
Infl	SSZ	Etan	CyA	Pall	HCQ	AZA	GST	LEF	DPen	Ana	MTX
GST	Pall	HCQ	DPen	Infl	AZA	Ana	MTX	Etan	SSZ	LEF	CyA
DPen	CyA	Infl	GST	Ana	LEF	MTX	Etan	SSZ	AZA	HCQ	Pall

Each row represents a possible strategy

Initial Experiments with GA

- Select single “offspring” strategy
- Compare with random member of current population
- Replace if new strategy appears better on mean of 10,000 (virtual) patients

After 0 replications

Pall	SSZ	CyA	LEF	Etan	AZA	DPen	Ana	GST	MTX	HCQ	Infl
CyA	HCQ	MTX	Pall	GST	SSZ	Etan	DPen	LEF	AZA	Ana	Infl
AZA	SSZ	HCQ	Ana	Infl	Pall	DPen	Etan	MTX	GST	CyA	LEF
LEF	GST	CyA	Ana	Infl	MTX	HCQ	AZA	Pall	Etan	DPen	SSZ
CyA	Etan	Ana	Pall	HCQ	AZA	GST	DPen	LEF	MTX	SSZ	Infl
HCQ	SSZ	Etan	Pall	LEF	Infl	CyA	AZA	DPen	Ana	GST	MTX
CyA	MTX	HCQ	GST	LEF	Ana	Etan	DPen	Pall	AZA	SSZ	Infl
Infl	SSZ	Etan	CyA	Pall	HCQ	AZA	GST	LEF	DPen	Ana	MTX
GST	Pall	HCQ	DPen	Infl	AZA	Ana	MTX	Etan	SSZ	LEF	CyA
DPen	CyA	Infl	GST	Ana	LEF	MTX	Etan	SSZ	AZA	HCQ	Pall

After 100 replications

MTX	DPen	SSZ	HCQ	CyA	GST	Ana	Infl	LEF	AZA	Pall	Etan
SSZ	AZA	MTX	DPen	GST	HCQ	CyA	LEF	Ana	Pall	Infl	Etan
MTX	DPen	SSZ	HCQ	GST	Ana	LEF	Infl	CyA	AZA	Pall	Etan
MTX	SSZ	AZA	DPen	GST	HCQ	CyA	LEF	Ana	Pall	Infl	Etan
MTX	DPen	SSZ	CyA	HCQ	GST	Ana	LEF	Infl	AZA	Pall	Etan
MTX	AZA	SSZ	DPen	GST	HCQ	CyA	LEF	Ana	Pall	Infl	Etan
MTX	AZA	SSZ	DPen	CyA	HCQ	GST	LEF	Infl	Ana	Etan	Pall
MTX	SSZ	DPen	GST	LEF	HCQ	CyA	AZA	Ana	Pall	Infl	Etan
MTX	DPen	GST	HCQ	CyA	LEF	SSZ	Ana	Pall	AZA	Infl	Etan
MTX	DPen	SSZ	HCQ	GST	AZA	Ana	LEF	CyA	Pall	Etan	Infl

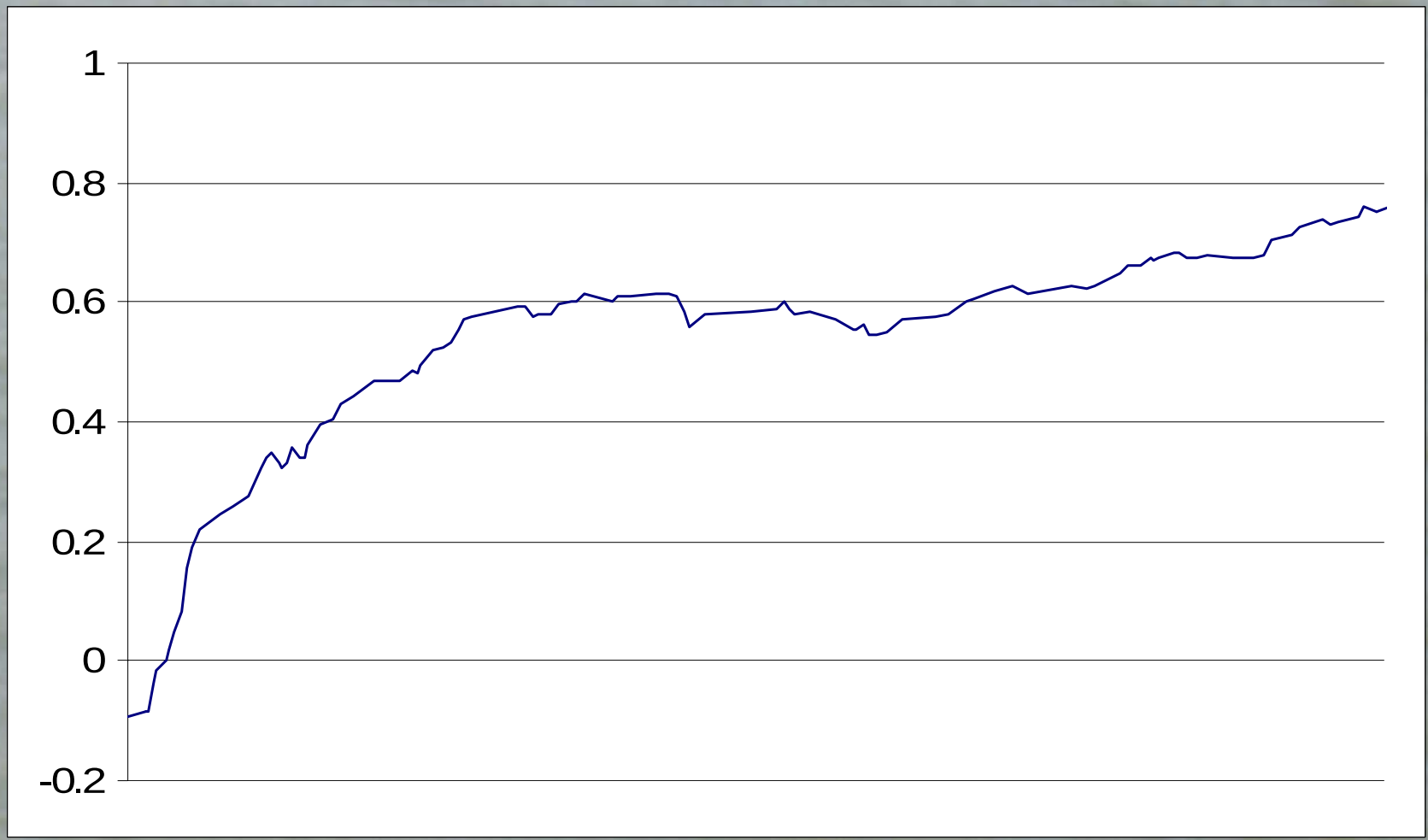
After 300 replications

MTX	SSZ	LEF	AZA	HCQ	GST	CyA	DPen	Infl	Etan	Pall	Ana
MTX	SSZ	LEF	HCQ	GST	DPen	AZA	CyA	Infl	Etan	Ana	Pall
MTX	SSZ	AZA	LEF	HCQ	GST	CyA	DPen	Infl	Etan	Ana	Pall
MTX	SSZ	LEF	HCQ	GST	DPen	AZA	CyA	Infl	Etan	Ana	Pall
MTX	SSZ	HCQ	LEF	CyA	GST	AZA	DPen	Infl	Etan	Ana	Pall
MTX	SSZ	AZA	LEF	HCQ	DPen	GST	CyA	Ana	Infl	Etan	Pall
MTX	SSZ	HCQ	LEF	GST	CyA	AZA	DPen	Infl	Etan	Ana	Pall
MTX	SSZ	LEF	HCQ	AZA	GST	DPen	CyA	Infl	Etan	Ana	Pall
MTX	SSZ	LEF	HCQ	GST	AZA	DPen	CyA	Infl	Etan	Ana	Pall
MTX	SSZ	LEF	HCQ	GST	AZA	DPen	CyA	Infl	Etan	Ana	Pall

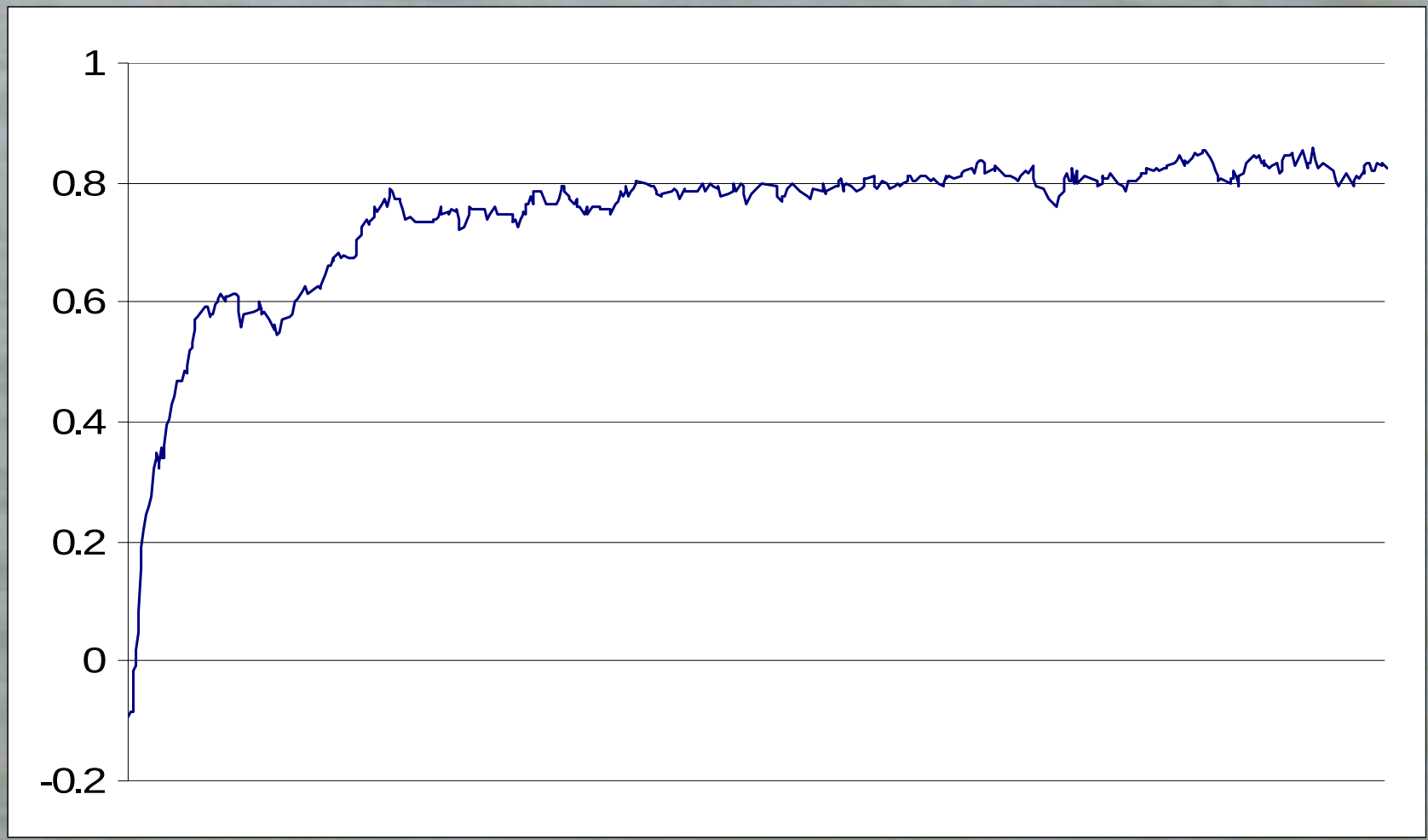
Measuring Progress

- Have no absolute measure of how good a strategy is
- Can compare any strategy with known optimal strategy
- Plot shows mean of rank correlation coefficient

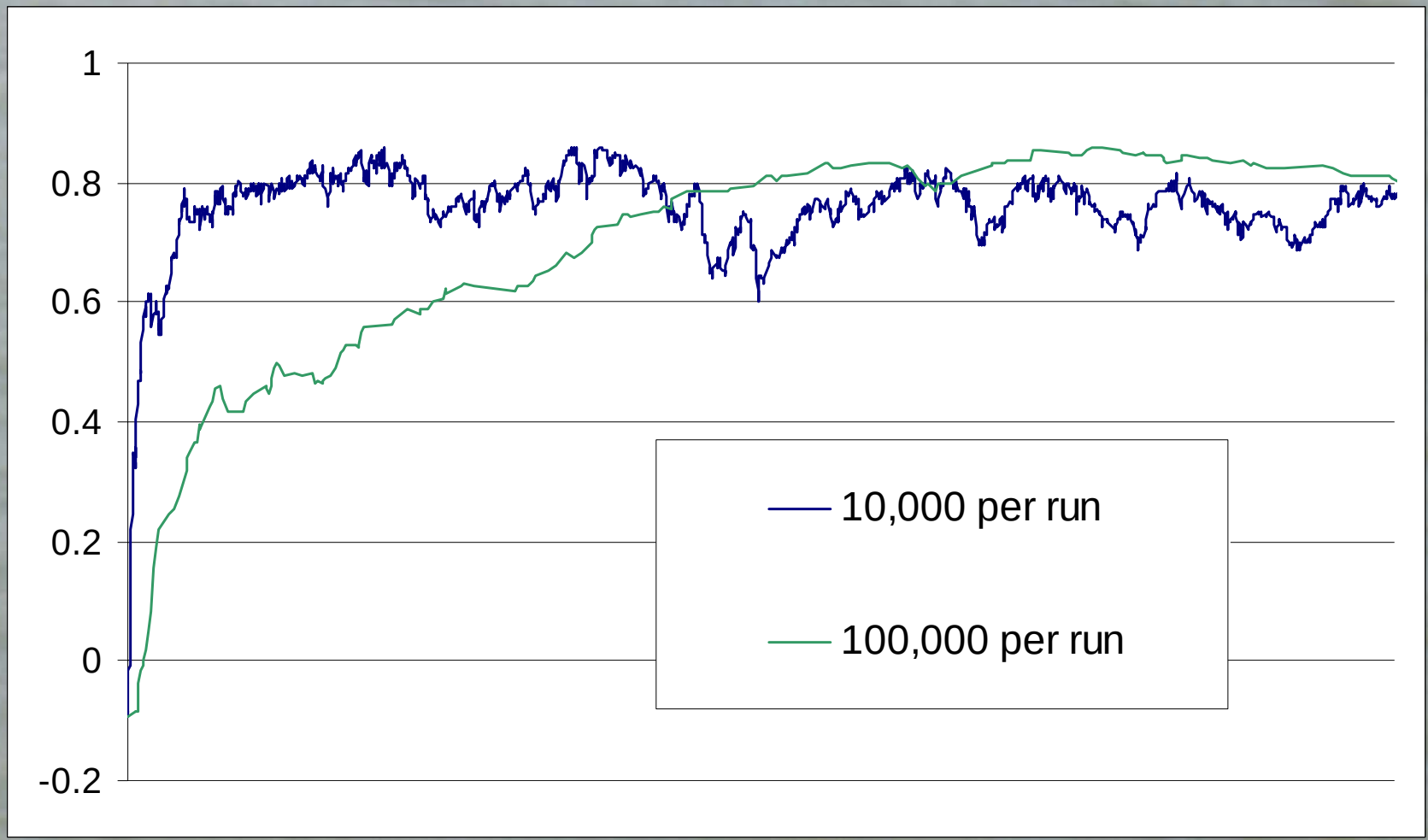
Progress of Genetic Algorithm



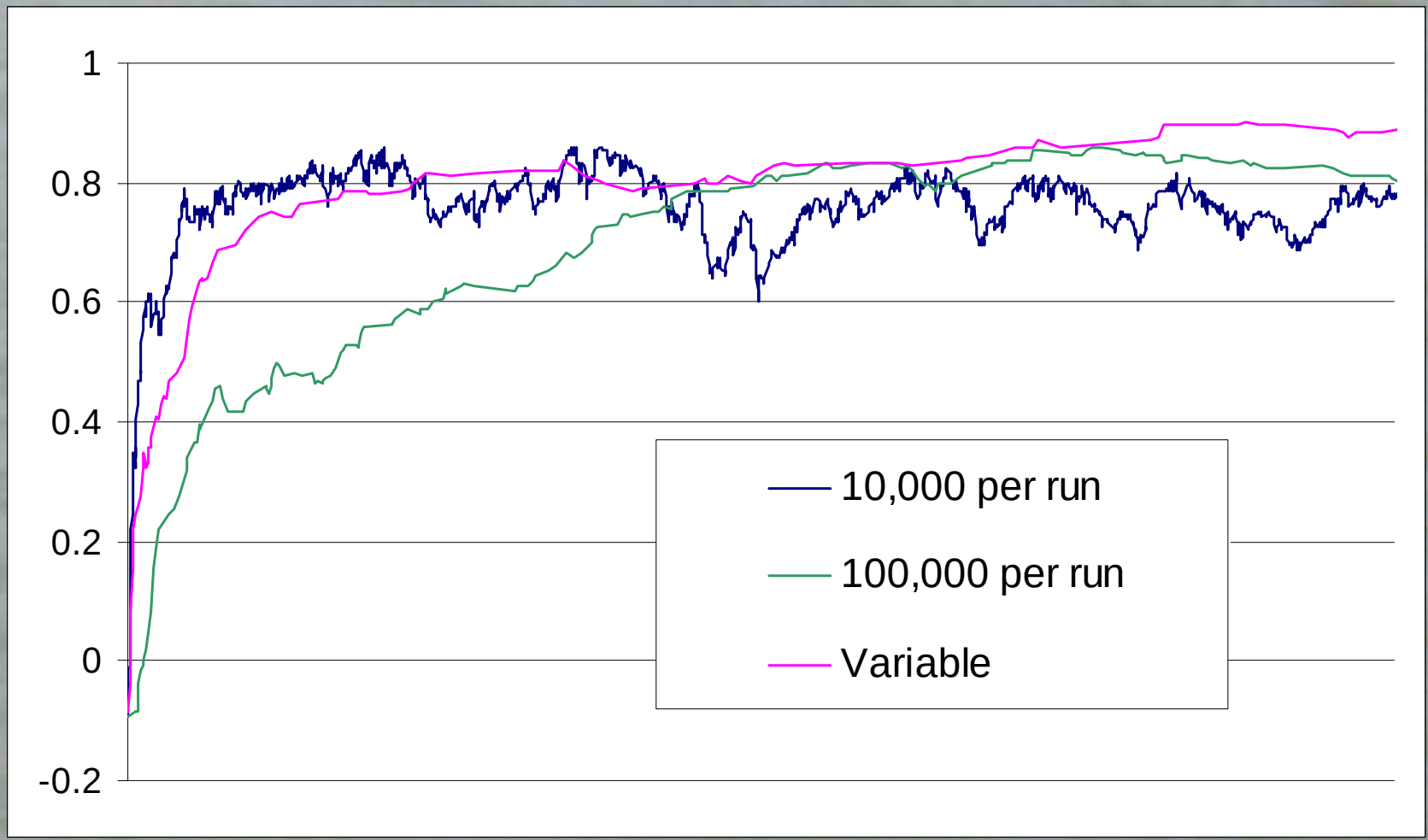
Progress of Genetic Algorithm 2



Increased Patients Per Run



Varying Patients Per Run



Conclusions from Case Study

- Genetic Algorithm (GA) can reach reasonably good solutions quickly
- Fixed numbers of patients per run not most efficient method
- Varying number of patients per run can be more efficient
- Borrow idea from Simulated Annealing: require greater certainty as GA proceeds

Any questions or suggestions?

Process of Genetic Algorithm 1

- Develop new strategy as “crossover” between two existing strategies

GST	Pall	HCQ	DPen	Infl	AZA	Ana	MTX	Etan	SSZ	LEF	CyA
HCQ	SSZ	Etan	Pall	LEF	Infl	CyA	AZA	DPen	Ana	GST	MTX

HCQ	Pall	Infl	AZA	DPen	Ana	GST	MTX	SSZ	Etan	LEF	CyA

Process of Genetic Algorithm 2

- “Mutation” allows complete coverage of decision space