Sequential Experimentation by Evolutionary Algorithms

Ofer M. Shir
Tel-Hai College and Migal Research Institute, Upper Galilee, Israel

Thomas Bäck
Natural Computing Group, Leiden University, The Netherlands

GECCO '19 Companion, July 13–17, 2019, Prague, Czech Republic

ACM ISBN 978-1-4503-6748-6/19/07.
https://doi.org/10.1145/3319619.3323381

1

Instructors

- **Ofer Shir** is a Senior Lecturer at the Computer Science Department in Tel-Hai College, and a Principal Investigator at Migal-Galilee Research Institute, where he heads the Scientific Informatics and Experimental Optimization group – both located in the Upper Galilee, Israel.

- **Thomas Bäck** is Professor of Computer Science at the Leiden Institute of Advanced Computer Science (LIACS), Leiden University, The Netherlands, where he is head of the Natural Computing group since 2002.

Contributors and former-instructors:

- **Joshua Knowles**, University of Birmingham, UK.
- **Richard Allmendinger**, University of Manchester, UK.

2

Agenda

1. What do we mean by "Sequential Experimentation"?
2. Examples of what has been done
3. Potential Application Areas
4. Reference: Statistical Design of Experiments
5. Case-Study: Quantum Control Experiments
6. Hot off the lab-bench: Protein Expression
7. Discussion: Conclusions and Open Questions

3

What do we mean by …

SEQUENTIAL EXPERIMENTATION

1

4

“Typical” Characteristics

- Experiments are time-consuming
- Experiments are expensive
- Evaluations can also be subjective (human experts)
- Only few experiments are possible
- There are exceptions as well!

Quantum Control: Case-Study

- Evolution “in the loop”
- Thousands of experiments possible (“*kHz regime*”)

5

Further Challenges

- Noise and uncertainty of measurements
- Multiple objectives
- Dynamically changing requirements of experimentalists / stakeholders!
- Dynamically changing (resource) constraints
- Cost choices during optimization
  ➔ Some experiments may cost more than others
- Unusual constraints on population sizes, other hyperparameters

6

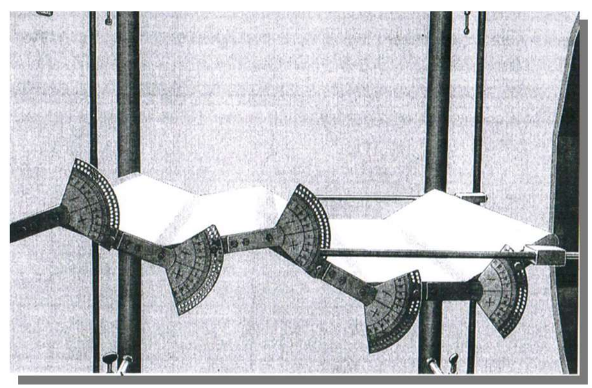
1960s … … … 2010s

Examples:
- Flow Plate
- Bended Pipe
- Nozzle
- Nutrient Solutions
- Coffee Formulations
- Quantum Control
- Protein Expression

EXAMPLE APPLICATIONS

7

Early Experiments I: Flow Plate



- A plate with 5 controllable angle brackets
- Measurable air flow drag (by a pitot tube)

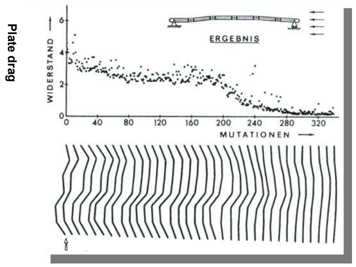
Figure from: I. Rechenberg, Evolutionsstrategie ’73, frommann-holzboog, Stuttgart 1973

8

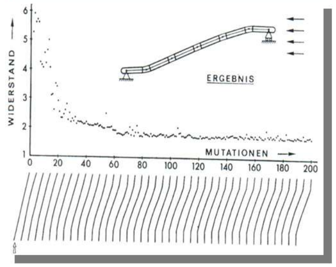
Early Experiments I: Flow Plate

Experiment 1:
- Left / right supporting point at same y-coordinate.
- Horizontal flow.
- Minimize drag.

Experiment 2:
- Left supporting point 25% lower than right one.
- Horizontal flow.
- Minimize drag.



Number of mutations and selected plate shapes



Number of mutations and selected plate shapes

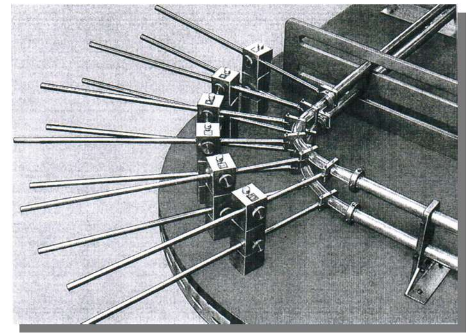
Start	-30	-40	40	-30	40
End	0	4	0	6	-6

Start	0	0	0	0	0
End	16	6	2	0	-18

Figures from: I. Rechenberg, Evolutionsstrategie ´73, frommann-holzboog, Stuttgart 1973

9

Early Experiments II: Bended Pipe

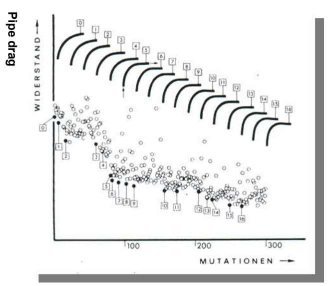


- A flexible pipe with 6 controllable bending devices
- Minimize bend losses of liquid flow
- Measure drag by pitot tube

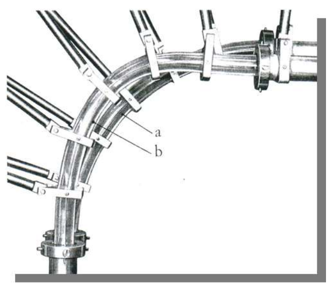
Figure from: I. Rechenberg, Evolutionsstrategie ´73, frommann-holzboog, Stuttgart 1973

10

Early Experiments II: Bended Pipe



Number of mutations and selected pipe shapes



Initial (a) and optimized (b) pipe shape

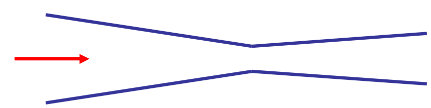
- Bend loss of final form reduced by 10%
- Including drag a total reduction of 2%

Figure from: I. Rechenberg, Evolutionsstrategie ´73, frommann-holzboog, Stuttgart 1973

11

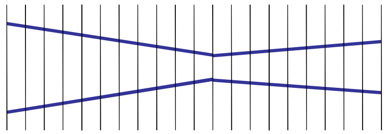
Early Experiment III: Nozzle

- What can be done if physics, (bio-) chemistry, … of process unkown?
- No model or simulation program available!
- Idea: Optimize with the real object
- “Hardware in the loop”
- Example: Supersonic nozzle, turbulent flow, physical model not available.



12

Experimental Setup: Nozzle

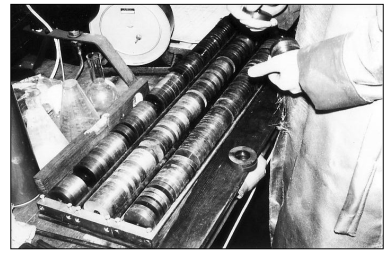


- Production of differently formed conic nozzle parts (pierced plates).
- Form of nozzle part is value of decision variable.

choosing conic nozzle parts (by EA)
clamping of conic nozzle parts (manually)
steam under high pressure passed into nozzle
degree of efficiency is **measured!**

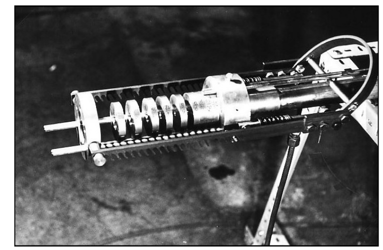
„simulator replacement“

Nozzle Experiment (I)



collection of conical nozzle parts

device for clamping nozzle parts



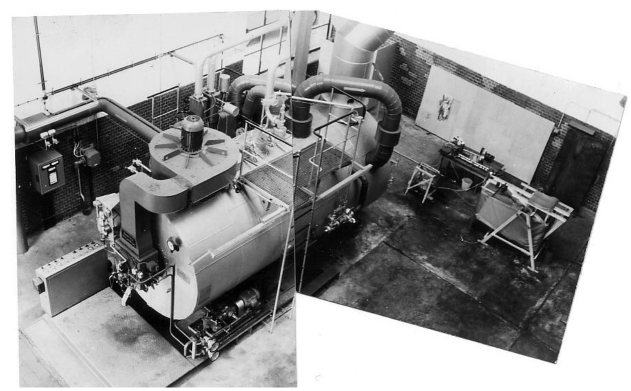
Figures courtesy of Hans-Paul Schwefel

Nozzle Experiment (II)

Hans-Paul Schwefel
while changing nozzle parts

Figures courtesy of Hans-Paul Schwefel

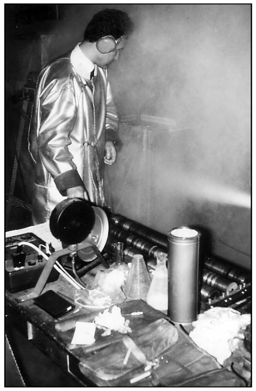
Nozzle Experiment (III)

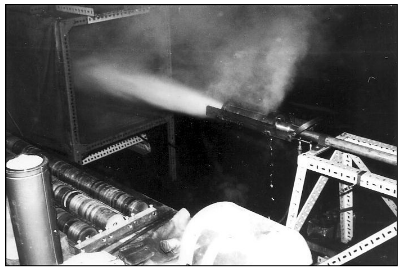


steam plant / experimental setup

Figures courtesy of Hans-Paul Schwefel

Nozzle Experiment (IV)





the nozzle in operation …

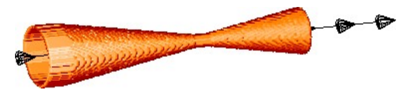
… while measuring degree of efficiency

Figures courtesy of Hans-Paul Schwefel

17

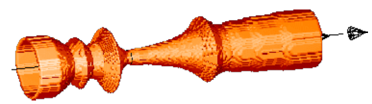
Nozzle Results (I)

- Illustrative Example: Optimize Efficiency
  - Initial:



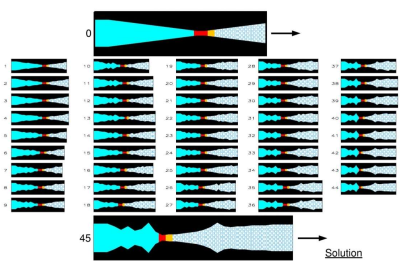
  - Evolution:

- 32% Improvement in Efficiency !



18

Nozzle Results (II)

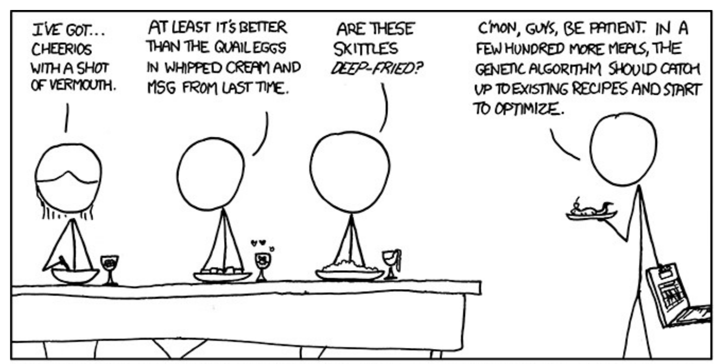


- 250 experiments were made.
- 45 improvements found.
- Discrete ring segments, variable-dimensional optimisation
- Gene duplication and deletion as additional operators.

J. Klockgether and H.-P. Schwefel, “Two-phase nozzle and hollow core jet experiments,” in Proceedings of the 11th Symposium on Engineering Aspects of Magneto-Hydrodynamics, Caltech, Pasadena, California, USA, 1970.

19

Experiment: Coffee Formulations

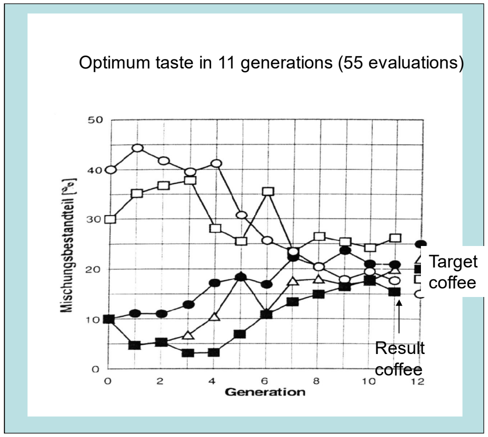


WE'VE DECIDED TO DROP THE CS DEPARTMENT FROM OUR WEEKLY DINNER PARTY HOSTING ROTATION.

M. Herdy: Beiträge zur Theorie und Anwendung der Evolutionsstrategie, PhD Thesis, Technical University of Berlin, Germany, 2000.

20

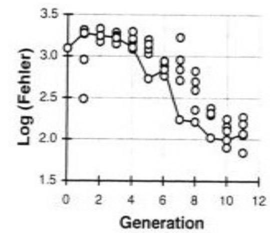
Coffee Formulations: Results



M. Herdy: Beiträge zur Theorie und Anwendung der Evolutionsstrategie, PhD Thesis, Technical University of Berlin, Germany, 2000.

Coffee Formulations: Results

- Coffee mixture differs a lot from target coffee !
- Taste is identical !
- Multiple realizations, but cost optimal !
- Approximation of cubic polynomial: 35 evals.



M. Herdy: Beiträge zur Theorie und Anwendung der Evolutionsstrategie, PhD Thesis, Technical University of Berlin, Germany, 2000.

EXPERIMENTAL OPTIMIZATION: FUNDAMENTALS

2

Experimental Requirements (for an Optimizer)

1. Speed: fast convergence is required
2. Reliability: reproducibility of results within a margin
   - Environmental parameters often hidden (temperature, pressure, …)
3. Robustness: manufacturing feasibility
4. Reference solution (recommended):

   pre-designed reference item, robust and stable, having a known objective function value

Convergence Speed

- Experiments are typically expensive:

Goal: Drive the system towards finding large improvements with as few experiments as possible.

- Practical solutions: “greedy” variants of evolutionary algorithms, e.g.,
  - Derandomized evolution strategies
  - ParEGO
  - Often “stochastic gradient search”
  - Need to support parallel execution!

25

Reliability of Results

- Mostly *algorithm-dependent*
- Attained results must be reproducible
- Scenarios of recording *experimental outliers* must be avoided (elitism is tricky…)
- Perceived result versus *a posteriori* result
- Possible solutions:
  - Employing comma (non-elitist) strategies
  - In ES, the recombination operator assists in treating noise (The Genetic Repair (GR) Hypothesis, Beyer)
  - Increasing sampling rate of measurements (“signal averaging”)

26

Environmental Parameters

- As many as possible physical conditions should be recorded during the experiment
- Ideally, sensitivity of the system to the environment should be assessed
- Basic starting points: recording Signal/Noise, extracting power spectrum of the noise, etc.

27

Manufacturing Feasibility

- Mostly *system-dependent*
- Realization of the prescribed decision parameters of the experiment to equivalent systems, e.g., in a manufacturing stage
- To this end, sensitivity of the system must be assessed (electronics, for instance)
- Upon obtaining reproducible results, they should be verified on equivalent systems

28

Noise “Colors”

Autocorrelation of the noise spectrum indicates the “memory property” of the disturbance –

- White Noise: ${}^{1}/_{f^0} \rightarrow \delta(t)$ (no correlation)
- Pink (Flicker) Noise: ${}^{1}/_{f^1} \rightarrow \text{unknown}$
- Red (Brownian) Noise: ${}^{1}/_{f^2} \rightarrow e^{-\lambda t}$ (exp. distribution)

Tip: Assess the stability of your system by extracting the Power Spectral Density of its signal-free state.

M. Roth, J. Roslund, and H. Rabitz, “Assessing and managing laser system stability for quantum control experiments”, *Rev. Sci. Instrum.* ***77****, 083107 (2006)*

29

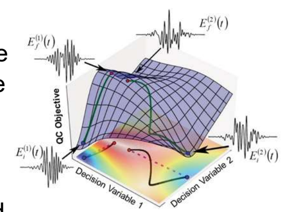
APPLICATION AREAS

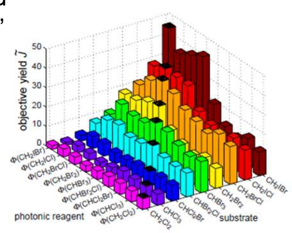
3

30

Basic Science: Discoveries as Combinatorial Optimization Problems

- A problem shared by scientists is to achieve optimal behavior of their systems and arrive at new discoveries while searching over an array of parameters
- It is commonly visualized in terms of a ‘*landscape*’: a candidate solution is mapped onto a ‘*position*’, its quality onto an ‘*altitude*’
- The task becomes to *efficiently navigating within this search-space,* which **scales exponentially with the number of variables**





Kell, D.B., *Scientific discovery as a combinatorial optimisation problem: How best to navigate the landscape of possible experiments?* BioEssays, 2012. **34**(3): 236-244.

31

A Classification

32

Potential Application Areas

- Cosmetics / Detergent Formulation Optimization
- Catalyst Formulation Optimization (Cost, Effectiveness, …)
- Subjective Evaluation Applications based on Human Taste or other Senses
- Engineering Applications Requiring Real-World Experiments for Measurement
- Concrete Formulation Optimization
- Glue Formulation Optimization
- Plant Startup Process
- Chemical Compound Synthesis Processes (e.g., Drugs)
- Instrument Setup Optimization

Reference/State-of-the-Art:

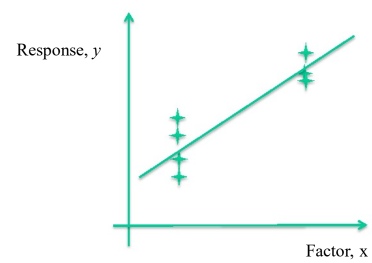
STATISTICAL DESIGN OF EXPERIMENTS

4

Introductory charts courtesy of Joshua Knowles.

DoE: The Industry's Golden Standard

Experimentation terminology



DoE
Response: also known as *effect*
Factor = independent variable
Factors have *levels*
A Factor at a particular level is a *treatment*
The regression line is a *model, fit* or *response surface*

Machine Learning
Factors are *features*
The response is the *class* or *output*

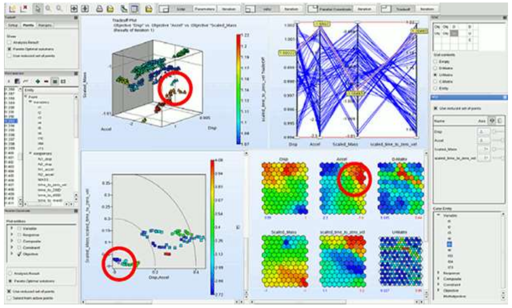
Optimization
Factors are *decision variables*
Response is *objective value, cost, benefit, utility* or *fitness*

Modern experiment 1

- *N* factors, *N*>>2, e.g. genes
- *M* effects, *M*>1, e.g. disease, + other effects
- *P*>1 nuisance factors, ages, gender, etc

- Possible Research Questions: which genes are *most responsible* for the disease, which groups of genes *work together*, and *are other effects involved* in explaining the disease?

Modern experiment 2



- Many factors
- Several effects
- Several nuisance variables
- Limited number of samples
- Noise (variance)
- Purpose: **Optimize** the effect

Classical DoE: topics

- OFAT
- Full factorial/Fractional factorial
- LHS
- Other designs

Handling multiple factors

- It is typical that we have *N*>1 factors to control
- The high-school solution to this is called

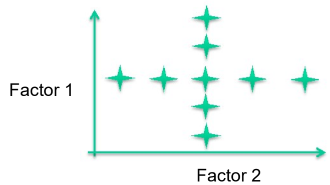
OFAT

(or one-factor-at-a-time)

- You hold all but one factor constant and vary that. Then you go onto the second factor ... and so on

OFAT

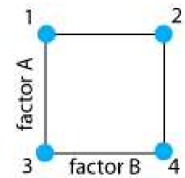
An OFAT design in two variables



Weaknesses of OFAT
1. OFAT requires more* runs for the same precision in effect estimation
2. OFAT cannot estimate interactions between factors
3. OFAT can miss optimal settings of factors

*compared with experimental designs like Plackett-Burman

Full Factorial design



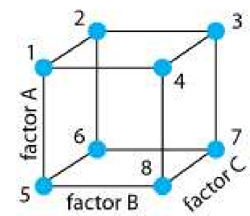
factor levels

trial	A	B
1	+	–
2	+	+
3	–	–
4	–	+

- : standard condition

+ : alternative value

(-, … , -) is the existing design

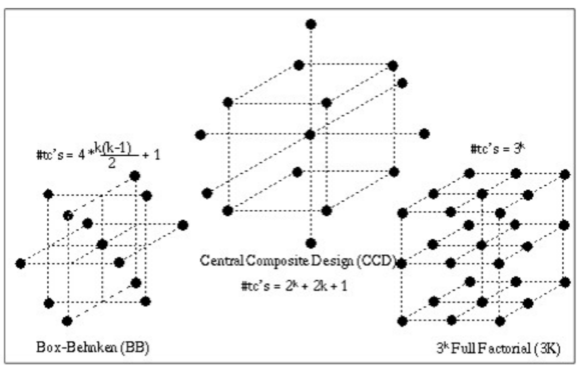


factor levels

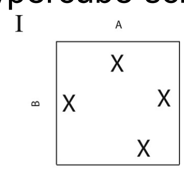
trial	A	B	C
1	+	–	–
2	+	–	+
3	+	+	+
4	+	+	–
5	–	–	–
6	–	–	+
7	–	+	+
8	–	+	–

- ANOVA and linear regression
- All interactions can also be identified
- → linear model

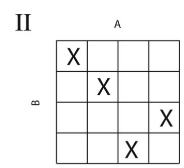
Other designs



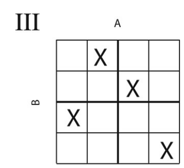
Latin hypercube screening design



Random design



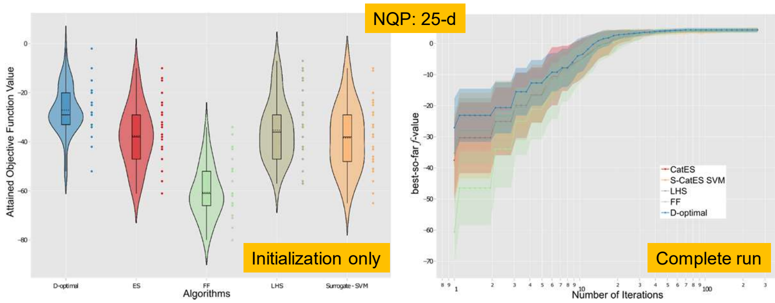
Latin Hypercube



Orthogonal

DoE vs. EAs on Combinatorial Optimization

- Comparing a Categorical ES, with/without *surrogates*, to modern DoEs
- Budget of ~2000 evaluations; discrete problems at dimensions $\{25,64,100\}$

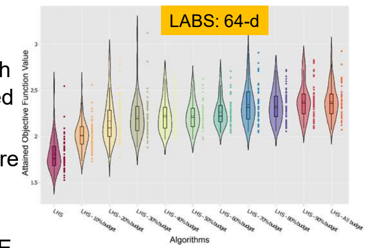


Horesh, N., Bäck, T., Shir O.M.: Predict or Screen Your Expensive Assay? DoE vs. Surrogates in Experimental Combinatorial Optimization. In: Proceedings of the Genetic and Evolutionary Computation Conference, GECCO-2019, New York, NY, USA, ACM Press (2019) To Appear

DoE vs. EAs on Combinatorial Optimization

Conclusions per the reported observations:

1) Using surrogate-aided iterative search was observed to perform best on such setups with a small budget.
2) DoE-initializations alone are inferior with respect to initializations that are followed by ES iterative search.
3) There is no evident gain in granting more than 30% of the budget on DoE-initializations.
4) D-Optimal was the most successful DoE methods on the low-dimensional setup, yet experiencing problem-dependent behavior.



Horesh, N., Bäck, T., Shir O.M.: Predict or Screen Your Expensive Assay? DoE vs. Surrogates in Experimental Combinatorial Optimization. In: Proceedings of the Genetic and Evolutionary Computation Conference, GECCO-2019, New York, NY, USA, ACM Press (2019) To Appear

Case-Study:

QUANTUM CONTROL EXPERIMENTS

5

Altering the Course of Quantum Phenomena

Rabitz et al.
"Electric Field Design"
Quantum Control Theory

$$i\hbar\frac{\partial}{\partial t}\left|\psi\left(t\right)\right\rangle = \mathcal{H}(t)\left|\psi\left(t\right)\right\rangle$$
$$\mathcal{H}\left(t\right) = \mathcal{H}_0 - \vec{\mu}\cdot\vec{\epsilon}\left(t\right)$$

Find optimal $\vec{\epsilon}\left(t\right)$ s.t.
$$\left|\left\langle\psi_{\mathrm{target}}\right|\psi\left(T\right)\right\rangle\right|^2 \longrightarrow \max$$

Hamiltonian required

PRA **37**, 4950 (1988)

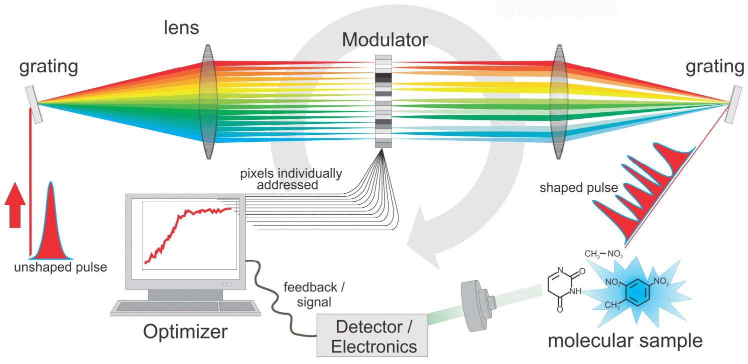
Judson and Rabitz
"Teaching Lasers to Control Molecules"
Quantum Control Experiments

Pulse Shaping $\xrightarrow{E(t)}$ Molecular Sample → Observation (detector) → Feedback (signal) → Optimization Routine $\xrightarrow{\text{modified } E(t)}$ Pulse Shaping

Hamiltonian **not** required

PRL **68**, 1500 (1992)

Quantum Control Experiments



The QCE Arena: The Optical Table

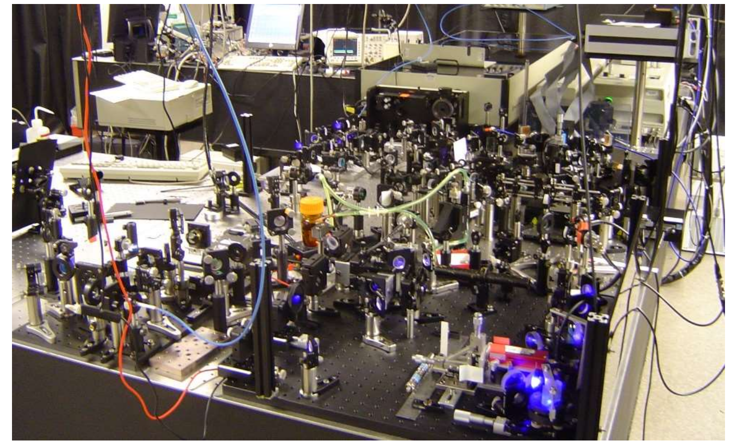


Figure courtesy of Jonathan Roslund

The Optical Table: Shaping the Pulse

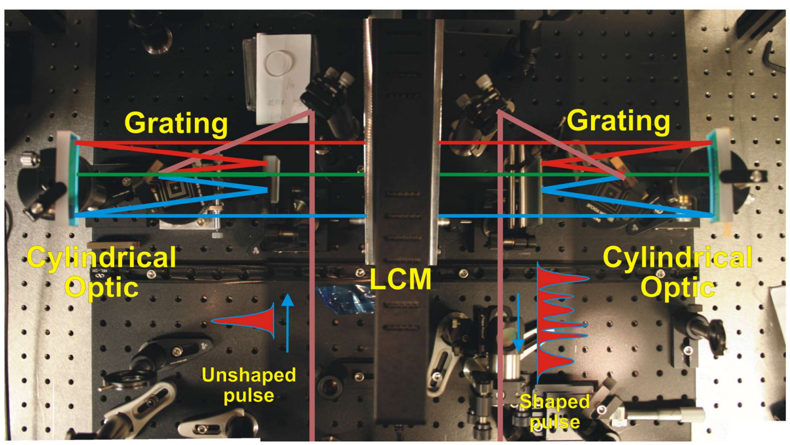
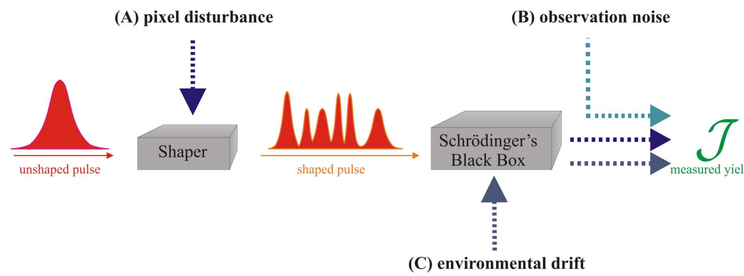


Figure courtesy of Jonathan Roslund

QCE: Sources of Noise/Uncertainty



(A) $\tilde{\phi}(\omega) = \left(\phi(\omega_1) + \mathcal{N}_1\left(0, \epsilon_S^2\right), \ldots, \phi(\omega_n) + \mathcal{N}_n\left(0, \epsilon_S^2\right)\right)$

(B) $\tilde{\mathcal{J}} = \mathcal{J} + \mathcal{N}\left(0, \epsilon_{\mathcal{J}}^2\right)$ Signal Averaging: $\left\langle \tilde{\mathcal{J}} \right\rangle = \mathcal{J}$, $\mathrm{VAR}\left[\tilde{\mathcal{J}}\right] = \frac{\epsilon_{\mathcal{J}}^2}{k}$

(C) $\hat{\mathcal{J}}(t) = \tilde{\mathcal{J}} + \xi(t)$

Single-Objective QCE

- CMA-ES was observed to perform extremely well with small population sizes
- Recombination is indeed necessary (GR, Beyer)
- Robust, reproducible, reliable solutions

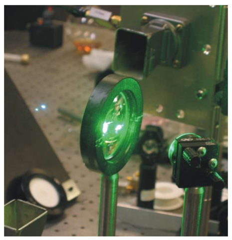


Figure courtesy of Jonathan Roslund

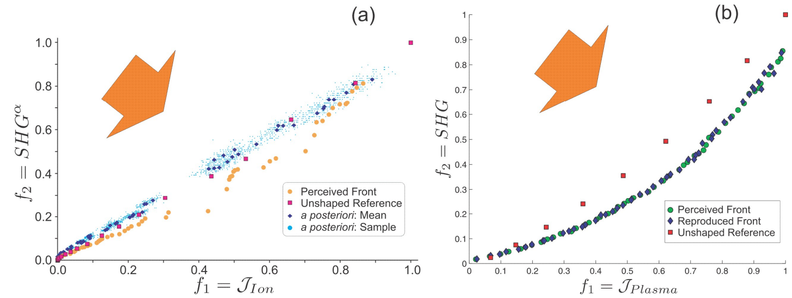
Roslund, J., Shir, O.M., Bäck, T., Rabitz, H.: Accelerated Optimization and Automated Discovery with Covariance Matrix Adaptation for Experimental Quantum Control. Physical Review A (Atomic, Molecular, and Optical Physics) **80**(4) (2009) 043415

54

Multi-Objective QCE

(a) Experimental Pareto frontier for the Total Ionization problem approximated by MO-CMA-ES, displaying the perceived frontier of a single experiment, the **reference frontier** of the intensity based non-shaped pulse, as well as a sampling of the Pareto optimal set.

(b) Experimental Pareto frontier for the Molecular Plasma Generation problem approximated by MO-CMA-ES remedied with occasional re-evaluation, displaying the perceived frontier, the reference frontier, and the reproduction of the Pareto optimal set.

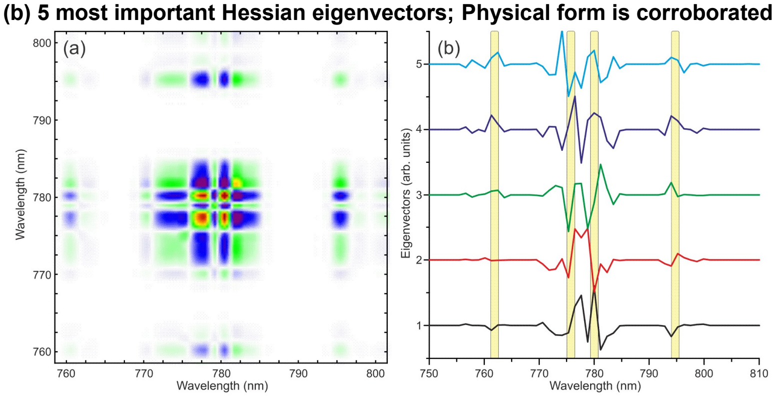


Shir, O.M., Roslund, J., Leghtas, Z., Rabitz, H.: Quantum Control Experiments as a Testbed for Evolutionary Multi-Objective Algorithms. Genetic Programming and Evolvable Machines **13**(4) (2012) 445—491

55

Extended Features: Statistical Learning (**FOCAL**)

(a) Retrieving the Hessian by FOCAL for rank-deficient atomic Rubidium
(b) 5 most important Hessian eigenvectors; Physical form is corroborated



Shir, O.M., Roslund, J., Whitley, D., Rabitz, H.: Efficient retrieval of landscape Hessian: Forced optimal covariance adaptive learning. Physical Review E **89**(6) (2014) 063306

56

Hot-off-the-lab-bench

PROTEIN EXPRESSION

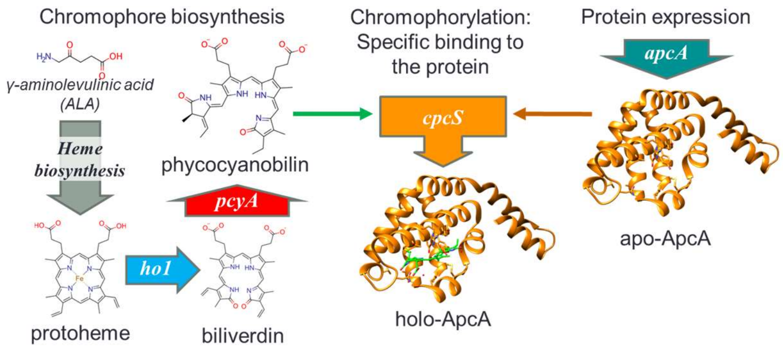
6

57

Heterologous Protein Expression

Four genes are required for ApcA heterologous expression in *E. coli*.

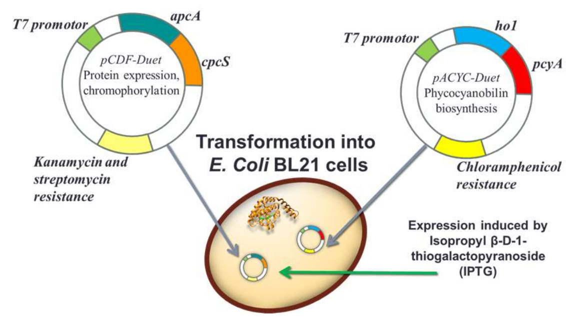
Goal: maximize the heterologous expression level



Erlich, Ch.: Experimental combinatorial optimization of phycobiliproteins' expression in *E.coli*. Thesis Tel-Hai College (2019).

58

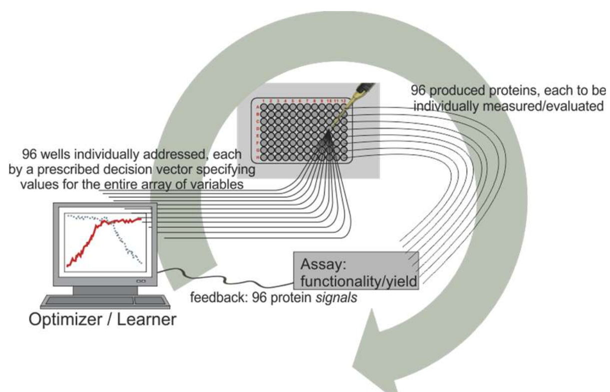
ApcA Expression System: Four Genes in Two Plasmids



- Controls (10 categorical decision variables):
  4 growth temp., 5 expression temp., 3 growth volumes,
  6 IPTG concent., 5 O.D. values, 4 induction durations,
  7 gamma-ALA concent., 2 gamma-ALA timings,
  11 FeCl_3 concent., 3 Medium types
- Search-space cardinality: ~3×10^6 possible combinations

59

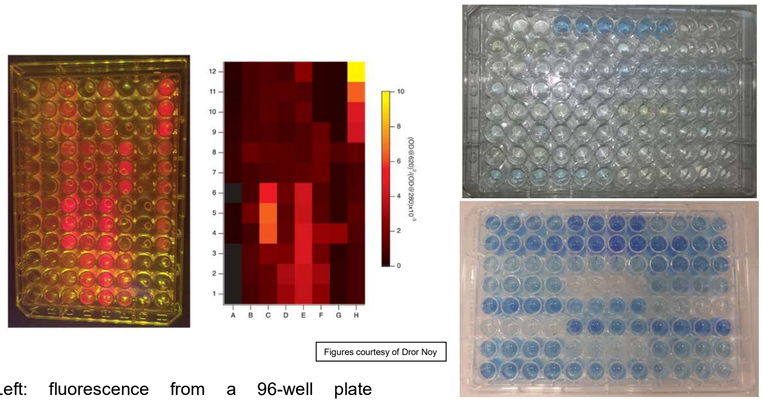
Closed Feedback Loop



A scheme of a typical single iteration (step) in a proposed optimization run of a production system. The input variables for each well are prescribed by the algorithm, whereas the output (feedback) of each produced molecule is provided by the assay - altogether closing a feedback loop.

60

ApcA Expression in *E. coli*: Assay

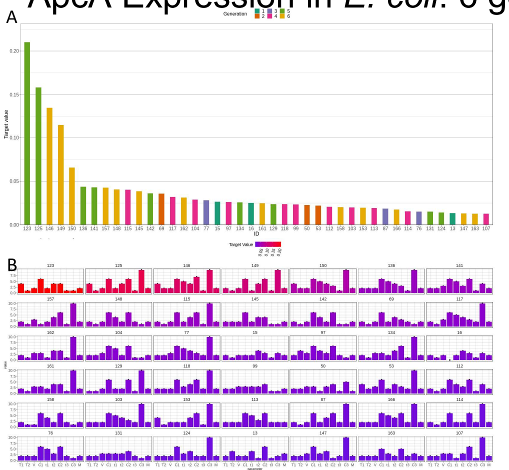


Left: fluorescence from a 96-well plate containing lysates of *E. coli* cells expressing ApcA. Right: evaluation of expression quality based on the ratio of absorption at 620nm vs. 280nm.

Images of the 1st and the 6th generation's collection plate, after cleaning and separating the proteins. The blue pigment is indicative of the expression strength.

61

ApcA Expression in *E. coli*: 6 generations



Top 25% combinations in terms of target values. **A.** Bar graph of the top 25% target values ordered from high to low values, colored by generation. **B.** A gallery of the combinations of the top 25% objective function values throughout the experimental campaign, depicting the explicit decision variables' values in bar-plots (the X-axis describes the decision variables and Y-axis shows their values). The color-map reflects the objective function values.

Erlich, Ch.: Experimental combinatorial optimization of phycobiliproteins' expression in *E.coli*. Thesis Tel-Hai College (2019).

62

7

DISCUSSION

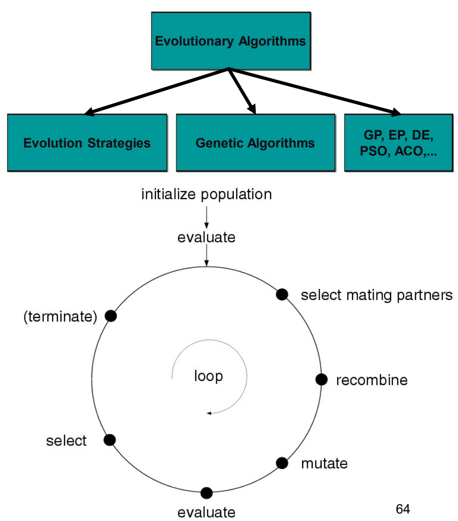
63

Evolutionary Algorithms Used

•Nozzle Experiments: Two-Membered Evolution Strategy [Rechenberg; 1973]

•Quantum Control Experiments: Derandomized Evolution Strategies [Hansen et al.; 1994-2008]

•Protein Expression Experiments: Categorical ES [unpublished]



64

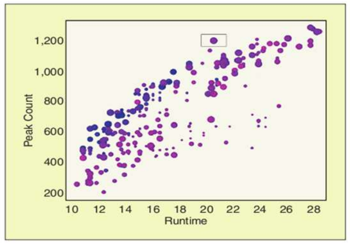
Some Practical Principles for Closed-Loop Optimization

- Keep experimentalists in the loop
- Understand the experimental platform
- Simulate the platform, and compare algorithms
- Do it for real – and get feedback

65

Keep experimentalists in the loop

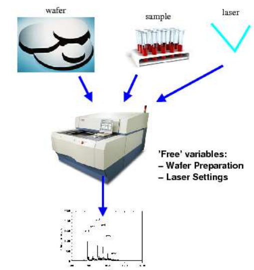
- Explain EAs, manage expectations of outcomes.
- Understand the variables and objectives. Confirm 3 times at least.
- Still be prepared to **change objectives** half-way through!
- Enable them to use familiar software for viewing results.



Objectives shown above were changed during optimization

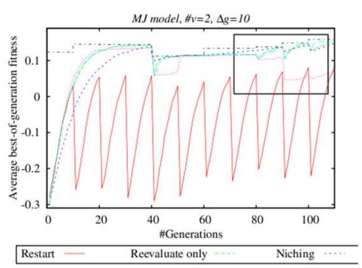
Understand the experimental platform

- Variables, constraints, measurements, noise
- Financial costs, time lags
- Resource constraints
- Batch size of platform dictates/constrains population size of EA



Simulations prior to the *real thing*

- Really helpful to manage expectations of stakeholders
- Tune your algorithms for weird and wonderful population sizes, constraints, budget limitations of real experimental platform
- If possible, use domain experts to design test problems that are similar to the real problem



Goals and Open Questions

- Experimental Optimization is hard – but an Evolutionary approach is feasible!
- Fundamental research in EAs is much needed:
  - Given a budget of ***k*** experiments – what strategy should be taken?
- NFL holds more than ever – there will be no winner algorithm handling all experimental scenarios!
- How do statistical approaches perform in comparison?
  - Especially *DoE*
- The comparison presented earlier is a fine starting point

Broader Picture: AI

- The Artificial Intelligence (AI) and Machine Learning (ML) revolution already takes place.
- No doubt that ML may boost scientific research by applying *pattern recognition*. But is that it?
- Some universities target this direction in education already at the BSc/MSc levels (CMU), stating that "*AI will drive more decisions in bio-experiments in the future*"

70

AI Prospects?

- The human/psychological factor among the experimentalists already plays a dominant role : shift the scientist/engineer's aim into explaining nature of solutions (mechanism!), rather than finding them
- But, existing hypotheses are already well-documented, plus there are established knowledge representation frameworks
- Next step?
  AI-based algorithm to formulate a scientific hypothesis and design experimentation

71

Acknowledgments

- Joshua Knowles
- Hans-Paul Schwefel
- Dror Noy
- Chen Erlich
- Naama Horesh
- Richard Allmendinger
- Herschel Rabitz
- Jonathan Roslund

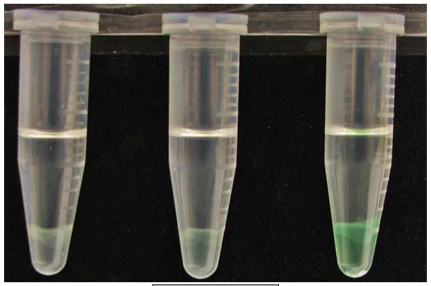


Figure courtesy of Dror Noy

72

Bibliography

- Allmendinger, R. and Knowles, J. (2013). On handling ephemeral resource constraints in evolutionary search. *Evolutionary Computation*, **21**(3):497–531.
- Bäck, T., Foussette, C., and Krause, P. (2013). *Contemporary Evolution Strategies*. Natural Computing Series. Springer-Verlag Berlin Heidelberg.
- Box, G. E., Hunter, J. S., and Hunter, W. G. (2005). *Statistics for Experimenters: Design, Innovation and Discovery*. John Wiley and Sons, Hoboken, NJ, USA, second edition.
- Eiben, A. E. and Smith, J. (2015). From evolutionary computation to the evolution of things. *Nature*, 521:476–482.
- Kell, D. B. (2012). Scientific discovery as a combinatorial optimisation problem: How best to navigate the landscape of possible experiments? *BioEssays*, **34**(3):236–244.
- Knowles, J. (2006). ParEGO: A Hybrid Algorithm with On-Line Landscape Approximation for Expensive Multiobjective Optimization Problems. *IEEE Transactions on Evolutionary Computation*, **10**(1):50–66.
- Knowles, J. (2009). Closed-loop evolutionary multiobjective optimization. *IEEE Computational Intelligence Magazine*, **4**(3):77–91.
- Rechenberg, I. (2000). Case studies in evolutionary experimentation and computation. *Computer Methods in Applied Mechanics and Engineering*, **186**(24):125–140.
- Roslund, J., Shir, O. M., Bäck, T., and Rabitz, H. (2009). Accelerated Optimization and Automated Discovery with Covariance Matrix Adaptation for Experimental Quantum Control. *Physical Review A*, **80**(4):043415.
- Shir, O. M., Roslund, J., Leghtas, Z., and Rabitz, H. (2012). Quantum control experiments as a testbed for evolutionary multi-objective algorithms. *Genetic Programming and Evolvable Machines*, **13**(4):445–491.
- Shir, O. M., Roslund, J., Whitley, D., and Rabitz, H. (2014). Efficient retrieval of landscape hessian: Forced optimal covariance adaptive learning. *Physical Review E*, **89**:063306.

73