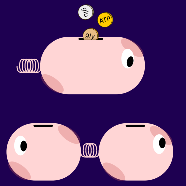
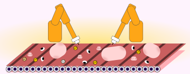
Economic Principles in Cell Physiology

Paris, July 4–6, 2022



Cell Models and Optimality

Wolfram Liebermeister & **Markus Köbis**



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Proclaimer

Economic Principles in **Cell Physiology**

Goals of this talk

- Motivate what is about to follow, i.e. the economy-of-the-cell analogy
- Establish ‘our’ view on ‘economic principles’, and ‘our’ subset of ‘cell physiology’
- Set the mathematical background (mostly: optimization) and cell modeling via the constraint-based framework

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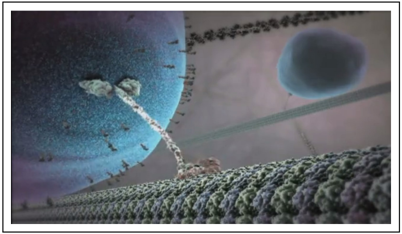
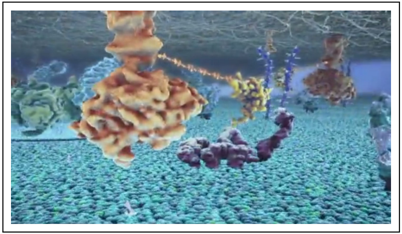
Non-goals/Beyond the book/talk





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(Molecular-) Simulation

- "High-level" physics and chemistry
- spatially distributed phenomena
- (Some) applications:
  - DNA folding
  - diffusion processes
  - information theory
- http://www.xvivo.net/animation/the-inner-life-of-the-cell

Outline

Book chapter "OPT"

1. Optimality principles in biology
2. History of mathematical optimality problems and their applications
3. Mathematical optimality problems
4. Examples of optimality problems in cells
5. Constraints and trade-offs in models: relation to empirical knowledge, mechanisms, and optimality
6. Multi-objective problems
7. Discussion: beyond optimality thinking

Outline of this session

1. Primer on Optimization
2. Connection to 'Economy' and 'Evolution'
3. 'Chapter 1': Primer on metabolic networks
4. Examples
5. Some historical notes
6. Discussion

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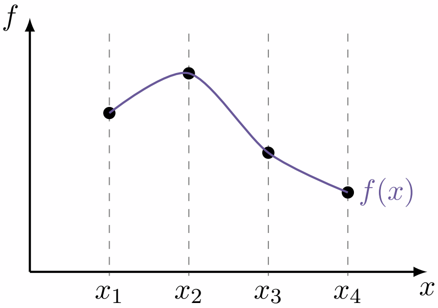
A Primer on Optimization

Optimization Problems (I)

Optimization problems (f. ex. 1-D)

Choose x such that some value $f(x)$ becomes maximal/minimal.



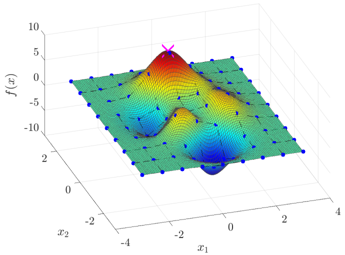
- 'Choose 'the best' out of possible decisions.'
- 'Find 'the best' possible configuration.'
- 'Pick 'the best', according to your preferences and/or quantifiable criteria.'

$$\min_{x \in S} f(x) \text{ or } \max_{x \in S} f(x)$$

Optimization Problems (II)

Optimization problems (f. ex. 2-D)

Choose $\boldsymbol{x}$ such that some value $f(\boldsymbol{x})$ becomes maximal/minimal.



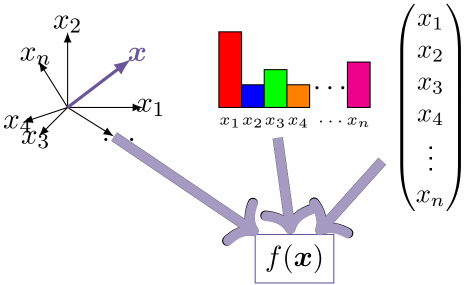
- 'Choose 'the best' out of possible decisions.'
- 'Find 'the best' possible configuration.'
- 'Pick 'the best', according to your preferences and/or quantifiable criteria.'

$$\min_{\boldsymbol{x} \in S} f(\boldsymbol{x}) \text{ or } \max_{\boldsymbol{x} \in S} f(\boldsymbol{x})$$

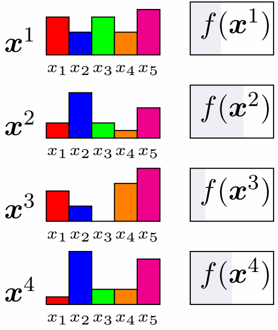
Optimization Problems (III)

$$\min_{\boldsymbol{x}\in S} f(\boldsymbol{x}) \text{ or } \max_{\boldsymbol{x}\in S} f(\boldsymbol{x})$$

Optimization Problems (f. ex. n-D)



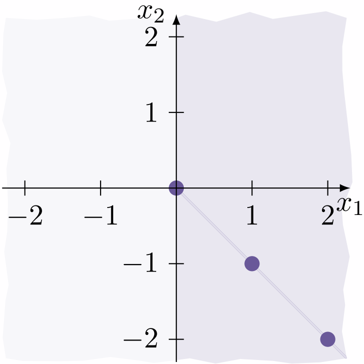
'Picking' the optimum



Optimization Problems (IV)

$$\min_{\boldsymbol{x} \in S} f(\boldsymbol{x}) \text{ or } \max_{\boldsymbol{x} \in S} f(\boldsymbol{x})$$

Constraining the Feasible Points



Constraint by means of

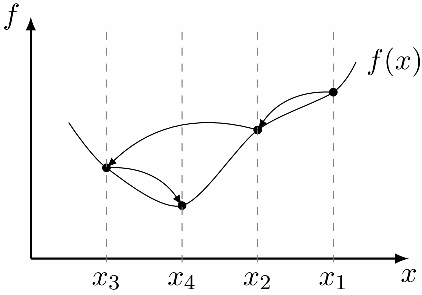
- (non-) linear inequalities
  $x_1 \geq 0$
- (non-) linear equalities
  $x_1 + x_2 = 0$
- set inclusions
  $x_2 \in \mathbb{Z}$

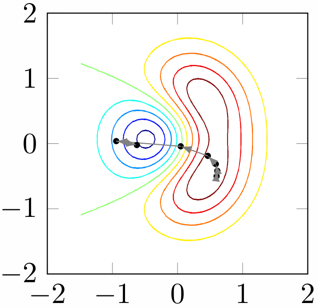
Optimization Algorithms: Some theory

Simplest Case: Gradient Descent for $\min_{\boldsymbol{x}} f(\boldsymbol{x})$

Iteration:

$$\boldsymbol{x}^{n+1} := \boldsymbol{x}^n - \nabla_{\boldsymbol{x}} f(\boldsymbol{x}^n)$$





If necessary: Gradient approximation:

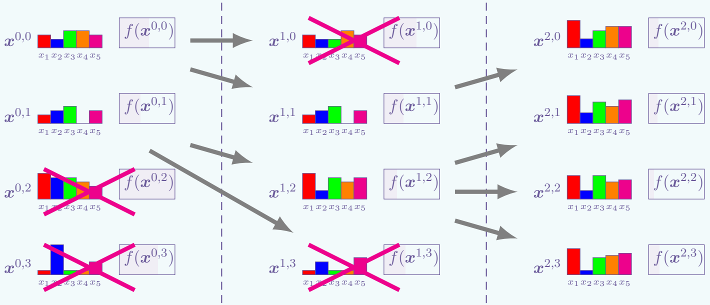
$$\frac{\partial f}{\partial x_i} \approx \frac{f(\boldsymbol{x} + h\boldsymbol{e}_i) - f(\boldsymbol{x})}{h}$$

Optimization Algorithms: Some theory

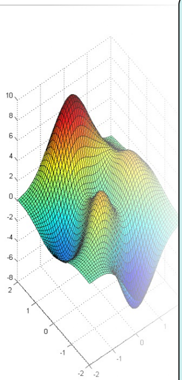
$$\min_{\boldsymbol{x}\in S} f(\boldsymbol{x}) \text{ or } \max_{\boldsymbol{x}\in S} f(\boldsymbol{x})$$

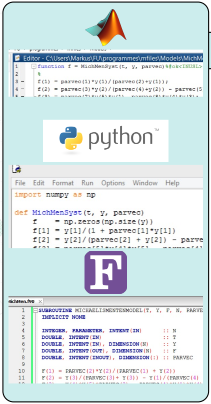
So-called 'genetic' (global optimization) algorithms

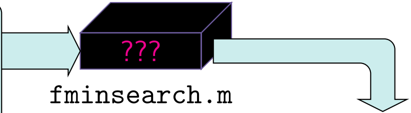
0. Pick a sample of initial guesses $\boldsymbol{x}^{0,0}$, $\boldsymbol{x}^{0,1}$, ...
1. Calculate function values
2. Sort out the worst cases, adapt/mix the best performers, goto 1.



Optimization Algorithms: 'Practice'







fminsearch.m

linprog.m

fmincon.m

scipy.optimize

cvxopt.py

APMonitor

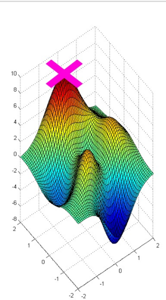
CPLEX

GUROBI

IPOPT

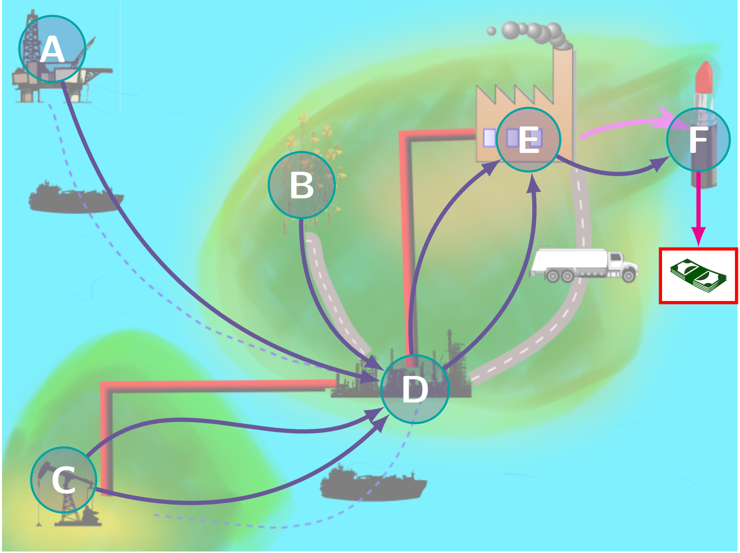
NLopt

⋮

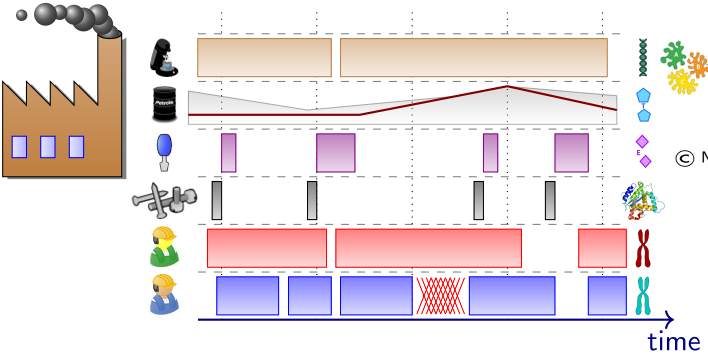


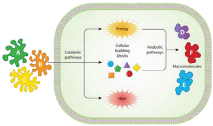
Connection to ‘Economy’ and ‘Evolution’

Our understanding of ‘economy’



Our understanding of ‘economy’





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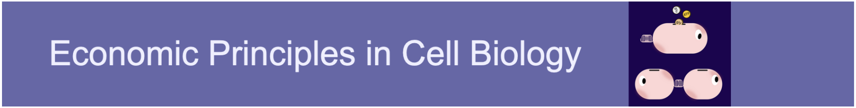
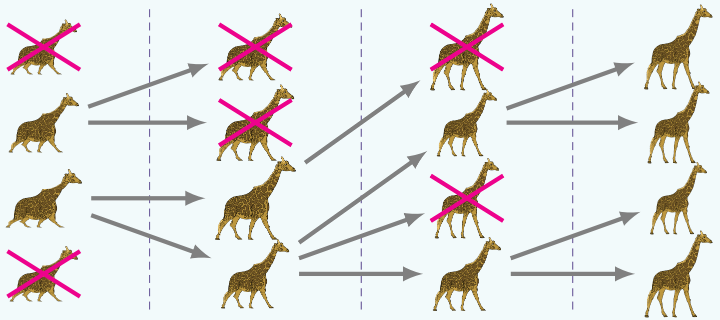


Evolution

"Case study 'Plant eater' " ;-)



Quintessentially

- Even if "Cells don't optimize", they have been optimized by evolution.
- "Optimization is the last religion in science."

Back to the Mentimeter

Evolution

filter ✓

chaos ✓

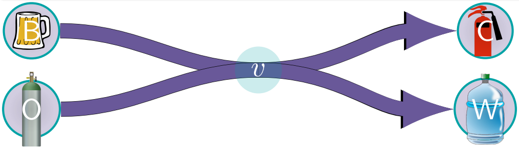
improvement ✓

optimization ✓

Primer on Metabolic Network Modeling

Metabolic Network Models

$$C_2H_5OH + 2\,O_2 \longrightarrow 2\,CO_2 + 3\,H_2O$$



Input-Output

B	1 out		
O	2 out		
C	2 in		
W	3 in		

$$\rightsquigarrow \begin{pmatrix} -1 \\ -2 \\ 2 \\ 3 \end{pmatrix} = \mathbf{S}$$

(Time-) Dynamical System

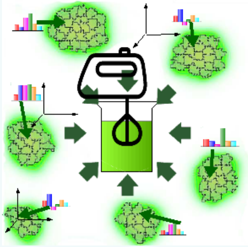
Description as an ODE/IVP

$$\dot{\boldsymbol{y}} = \mathbf{S} \cdot \boldsymbol{v}$$
$$\boldsymbol{y}(0) = \boldsymbol{y}_0$$

plus rate laws, enzymes, genes, regulation, etc.

Metabolic Network Models

The “well-stirred” metabolism



Dynamics

$$\dot{\boldsymbol{y}}(t) = \mathbf{S} \cdot \boldsymbol{v}(t)$$

$$\mathbf{0} = \mathbf{S} \cdot \boldsymbol{v}(t)$$

Flow dependent on quota

$3A + B \leftrightarrow C$

Simple rate laws

- Mass action: $f_i(t) \propto y_A^3(t) \cdot y_B(t)$ 

- Michaelis-Menten: $f_i(t) \propto \frac{y_A(t)}{y_A(t)+K_M}$ 

- Hill-function (act.): $f_i = \tilde{f}_i \cdot \frac{y_E^\alpha}{K^\alpha + y_E^\alpha}$ 

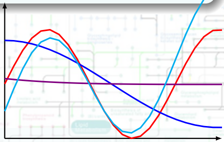
- Hill-function (inh.): $f_i = \tilde{f}_i \cdot \frac{K^\alpha}{K^\alpha + y_E^\alpha}$ 

(Quasi) Steady State Approximation

- Some reactions orders of magnitude faster than others
- Model assumption: Always at equilibrium.

Constraint-based Modeling

Continuous Description



$$\frac{\mathrm{d}y_i}{\mathrm{d}t} = \sum_{j=1}^{n} S_{ij} v_j$$

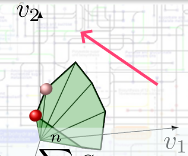
$$\Rightarrow \dot{\boldsymbol{y}} = \mathbf{S} \cdot \boldsymbol{v}(\boldsymbol{y}, \boldsymbol{p})$$

\+ Very accurate

\- Computationally expensive

\- Not sufficient information

'Constraint-Based'

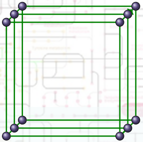


$$0 = \sum_{j=1}^{n} S_{ij} v_j$$

$$\Rightarrow \mathbf{S} \cdot \boldsymbol{v} = \mathbf{0}, \boldsymbol{lb} \leq \boldsymbol{v} \leq \boldsymbol{ub}$$

- Consider just the data 'you know'
- Add (consecutively) as constraints
- hard/soft constraints

Discrete Description



$$Y_i^{(n+1)} = \mathrm{IF}(Y_j^n \wedge \neg Y_i^n \vee \ldots)$$

$$\Rightarrow \boldsymbol{Y}^{(n+1)} = \boldsymbol{\Phi}(\boldsymbol{Y}^{(n)}; \boldsymbol{p})$$

\+ Single simulations easy

\- Very crude

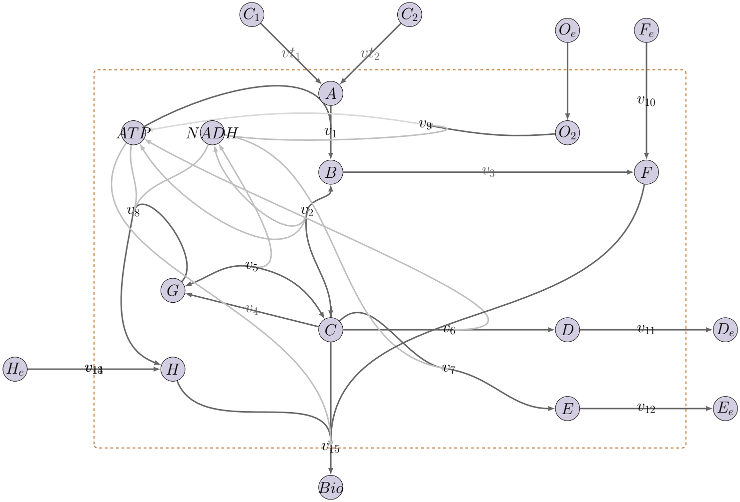
\- Just rough qualitative understanding

source: https://doi.org/10.3390/metabo3010001

Examples

Examples (I)

Tuesday: Flux Balance Analysis



Covert/Schilling/Palsson, 2001

Examples (I)

Flux Balance Analysis

- Collect what you know (stoichiometrics plus lower/upper flux bounds)
- Find flux distribution from linear optimization

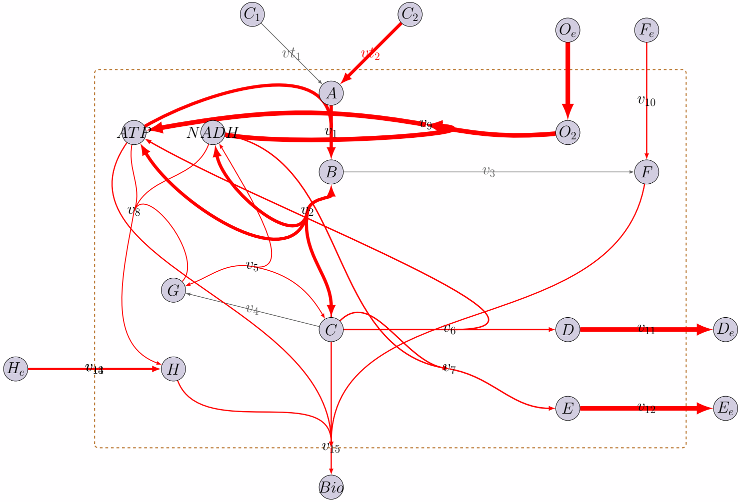
$$\max_{\boldsymbol{v}} f(\boldsymbol{v}) = \boldsymbol{b}^\top \cdot \boldsymbol{v}$$

$$\text{s.t. } \mathbf{0} = \mathbf{S} \cdot \boldsymbol{v}$$

$$\boldsymbol{lb} \leq \boldsymbol{v} \leq \boldsymbol{ub}$$

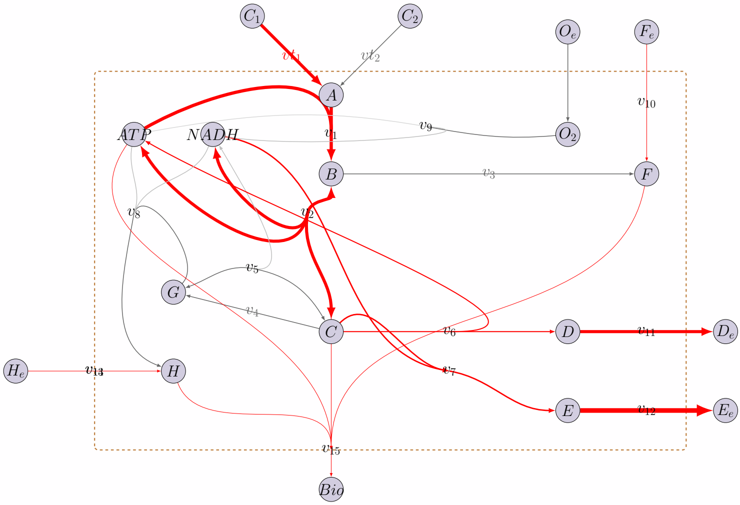
Examples (I)

Growth (i.e. Bio) maximization



Examples (I)

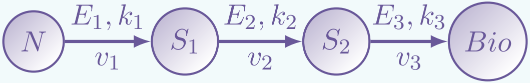
"E" maximization



Examples (II)

Optimal enzyme levels

A linear reaction chain



Klipp et al. 2002

Network's constraints: $\mathbf{S} \cdot \boldsymbol{v} = \mathbf{0}$, $\mathbf{0} \leq \boldsymbol{v}$

$$\boldsymbol{v} \leq \mathrm{diag}(k_1, k_2, k_3) \cdot \begin{pmatrix} E_1 \\ E_2 \\ E_3 \end{pmatrix}$$

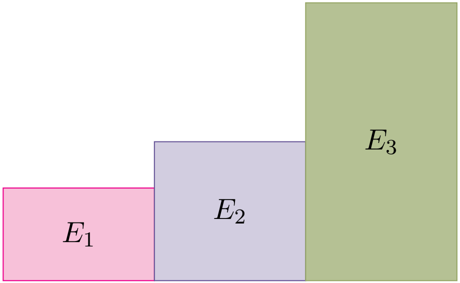
- Goal: Maximize growth reaction v_3
- 'Costs': Enzyme activation $E_1^2 + E_2^2 + E_3^2$

Examples (II)

Optimal enzyme levels

(Toy-) example: $k_1 = 3,\ k_2 = 2,\ k_3 = 1.$

$$J = \qquad (E_1^2 + E_2^2 + E_3^2) - \qquad v_3$$



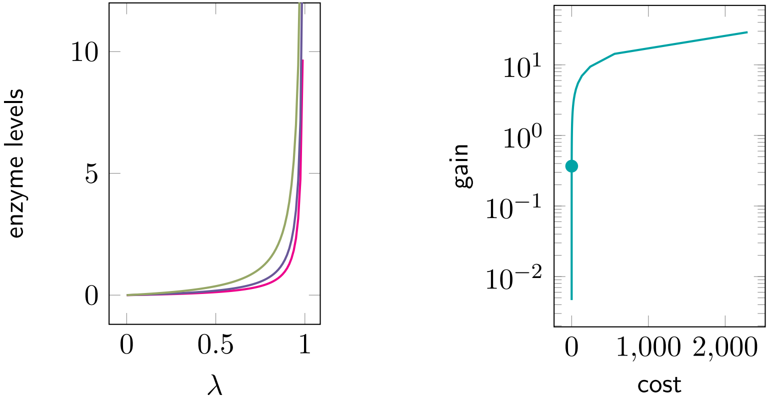
Gain:
0.3673
Cost:
0.3673

Examples (II)

Optimal enzyme levels

(Toy-) example: $k_1 = 3$, $k_2 = 2$, $k_3 = 1$.

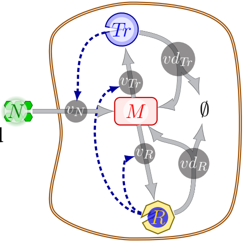
$$J = (1 - \lambda) \cdot (E_1^2 + E_2^2 + E_3^2) - \lambda \cdot v_3$$

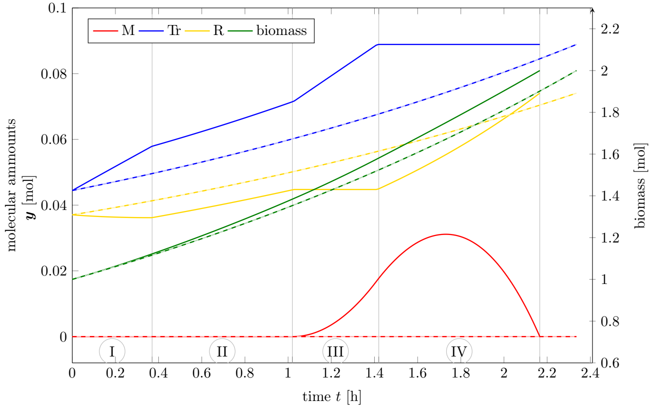


Examples (III)

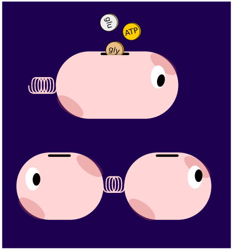
Wednesday: "Optimality in Time"

Time-optimal behavior in a self-replicator $J = t_{\text{end}}$





Köbis et al., 2022



Potential Objective Functions

Given: stoichiometrics, flux bounds, some dyn. data, ...

Biologically inspired optimization principles

1. Cell efficiency: "Minimize fluxes" ("Tikhonov regularization")

   $$J := \int \|\boldsymbol{v}(\cdot)\|_*^2 \mathrm{d}t \qquad \text{plus minimum growth conditions}$$

2. Growth (a): Maximize biomass/macro molecule production of the cells

   $$J := -\int \|\boldsymbol{w}_{\mathrm{obj}}(t)^\top \cdot \boldsymbol{y}(t)\|_*^2 \mathrm{d}t$$

3. Growth (b): Maximize flux through biomass reaction(s)

   $$J := -\int \|\boldsymbol{V}_{\boldsymbol{y}_{\mathrm{growth}}}(t)\|_*^2 \mathrm{d}t$$

4. Robustness (a, b): Maximize survival time, minimize response times

   $$J = -t_{\mathrm{end}} = -\int 1 \mathrm{d}t \quad \text{and cell survival}$$

5. Robustness (c): Maximize nutrient uptake

   $$J = -\int \|\boldsymbol{w}_{\mathrm{obj}}(t)^\top \cdot \boldsymbol{v}(t)\|_*^2 \mathrm{d}t$$

6. "Multiobjective" optimization, inverse optimality, etc.

Historical Notes

Historical Notes (I)

Optimization Methods in the Natural Sciences

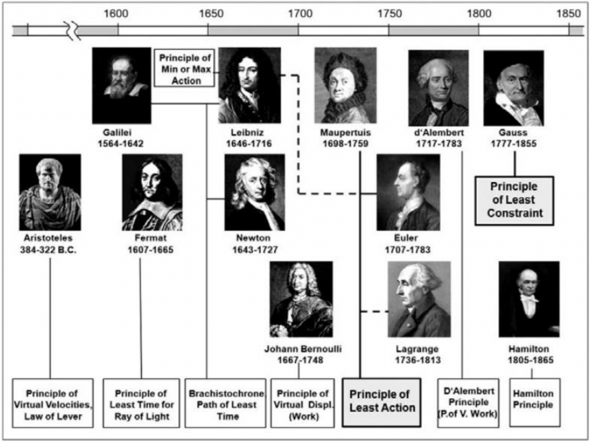


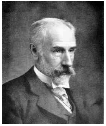
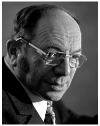
Fig. 1 Evolution of Extremum Principles.

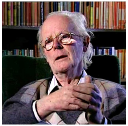
Ramm, E. (2011) GAMM-Mitteilungen 34(2), 164–182 (recommended by J. Banga)

Historical Notes (II)

Optimization Methods in Economy

- 1881: Edgeworth, *Mathematical Psychics*
- 1939: Production Planning using linear optimization (Kantorovich)
- 1939–1945: World War II (Operations Planning)
- 1944: von Neumann, Morgenstern, *Theory of games and economic behavior*
- 1947: Simplex Algorithm (Dantzig)
- 1954: Markowitz (quadratic programming, portfolio analysis, later: risk measures)
- 1973: Maynard, Price *The logic of animal conflict*

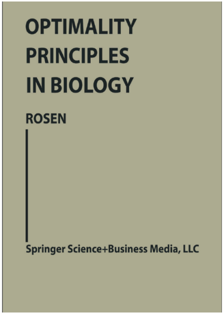



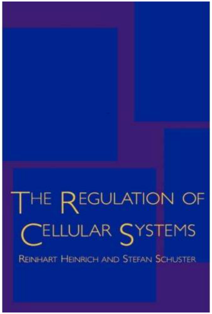
CC Wikipedia

Historical Notes (III)

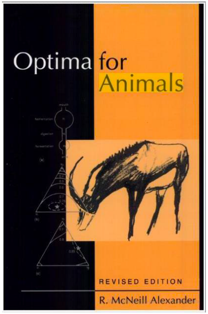
Optimization Methods in (Systems) Biology



1967



1996



1996

- Flux balance analysis: 1990
- (Modern) systems biology full established: 2000–2010

Concluding Remarks/Discussion

Conclusion (I)

Central issue: Lack of first principles in (systems) biology

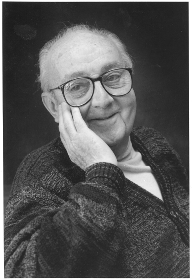
Optimization in Constraint-based Modeling

- Optimization itself not necessarily driving force but often as a proxy based on
  - the viewpoint of cells as 'economic actors'
  - "cells do not optimize", BUT "cells have been optimized by evolution"
- "Sometimes, things *look* optimal."

Optimization techniques go beyond this

In theory **and** application (e.g. network reconstruction, parameter fitting, a.i., multi-objective, game theory, robustness, inverse problems, control problems, etc.)

Conclusion (II)



'Essentially, all models are wrong, but some are useful.'

George Box, Norman Draper, Empirical Model-Building and Response Surfaces (1987) CC Wikipedia

Thank You!

Discussion

e. g. Mentimeter, part 2(?)

Economic goals from the bio-viewpoint?

Money ✓?

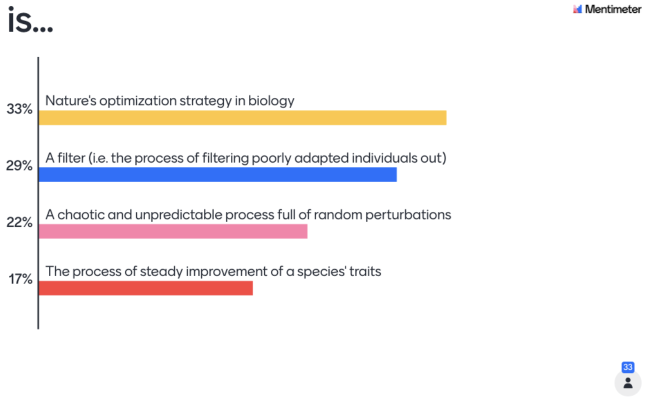
Survival/Competition ✓?

Long-term prosperity ✓?

Innovation/Sustainability ✓?

Efficiency ✓?

Evolution is...



The main goal of economic actions is...

Mentimeter

34

Image sources

matlab logo: https://se.mathworks.com/content/mathworks/se/en/company/newsletters/articles/the-mathworks-logo-is-an-eigenfunction-of-the-wave-equation/_jcr_content/mainParsys/image_2.adapt.full.medium.gif/1469941373397.gif
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