SSIP 2005

13th Summer School on Image Processing

30 June - 8 July 2005 • Szeged, Hungary

UNIVERSITAS SCIENTIARUM SZEGEDIENSIS

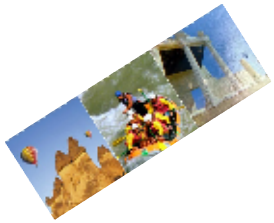
EUROPT

Challenges in the Optimization of Bio-Systems

Gerhard-Wilhelm Weber

Institute of Applied Mathematics, Middle East Technical University, Ankara, Turkey

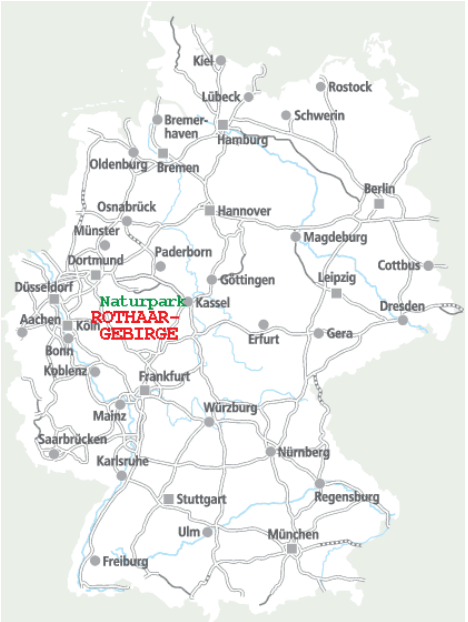
http://www.iam.metu.edu.tr/research/groups/compbio/index.html



Content

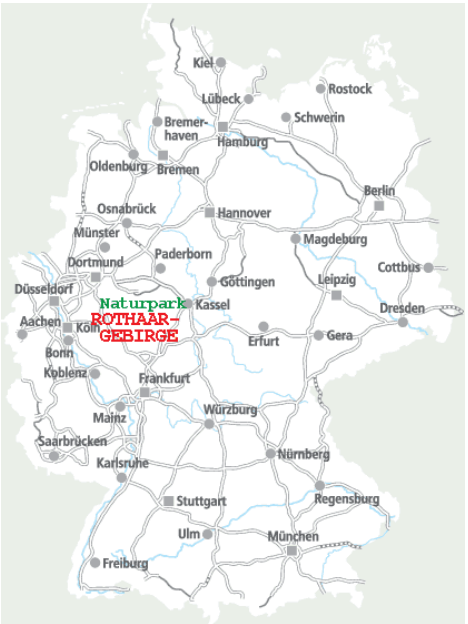
- Motivation: Bio-Systems
- Computational Biology
- Modeling and Prediction of Gene Expression Patterns
- Population Dynamics, Gene Dynamics and Variation
- Optimization
- Computational Metabolism, Medicine and Tomography
- Earth Warming and Sustainable Development
- Conclusion and Perspectives

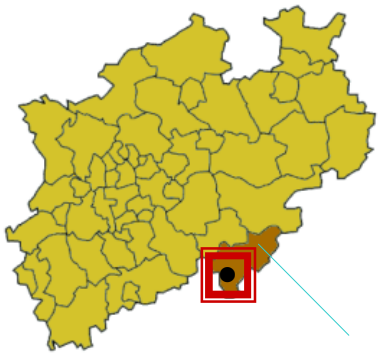
Bio-Systems



Bad Berleburg,
Wemlighausen

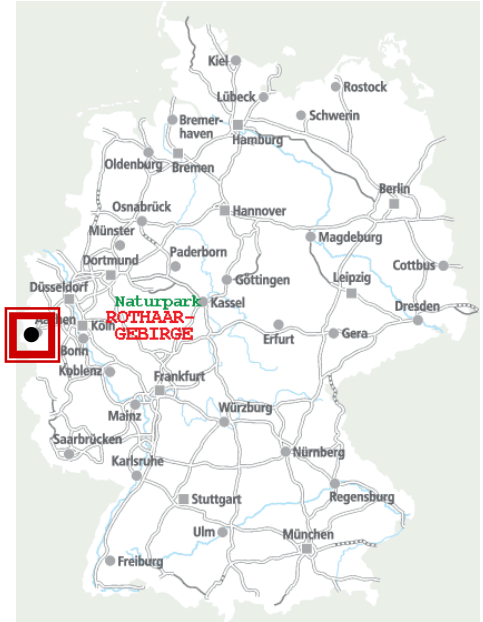
Bio-Systems





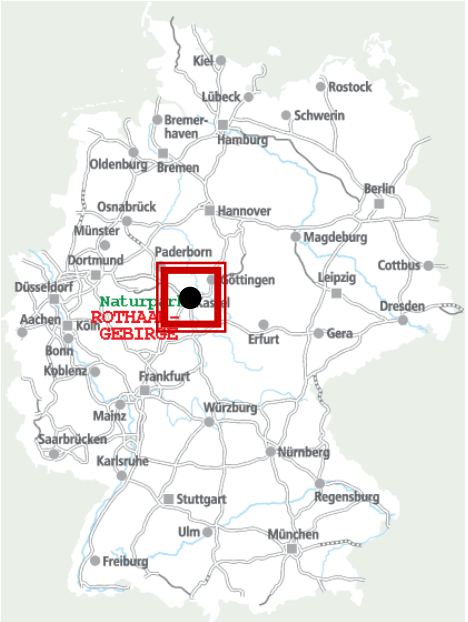
Bad Berleburg,
Wemlighausen

Bio-Systems



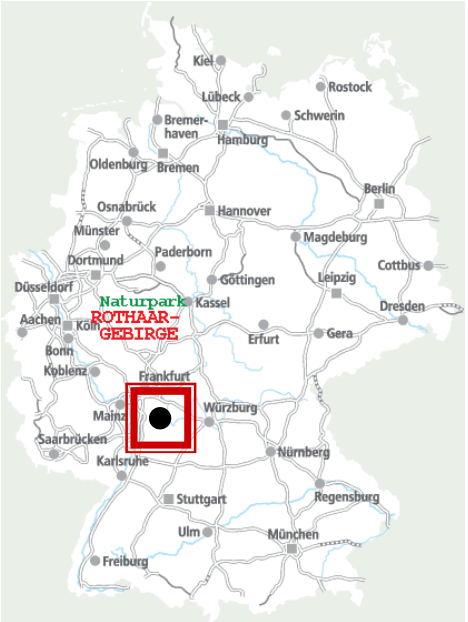
Bad Berleburg,
Wemlighausen

Bio-Systems



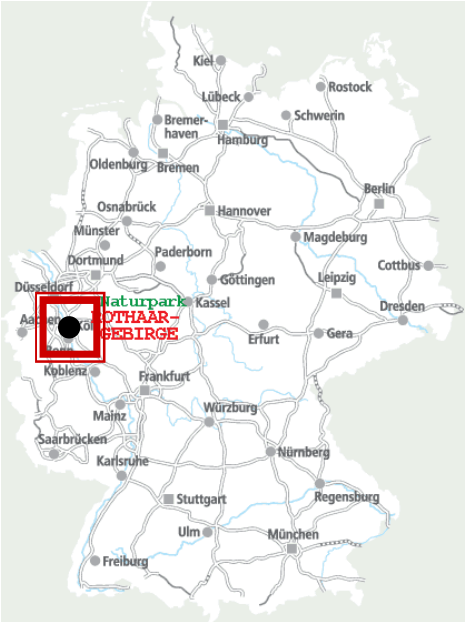
Bad Berleburg,
Wemlighausen

Bio-Systems



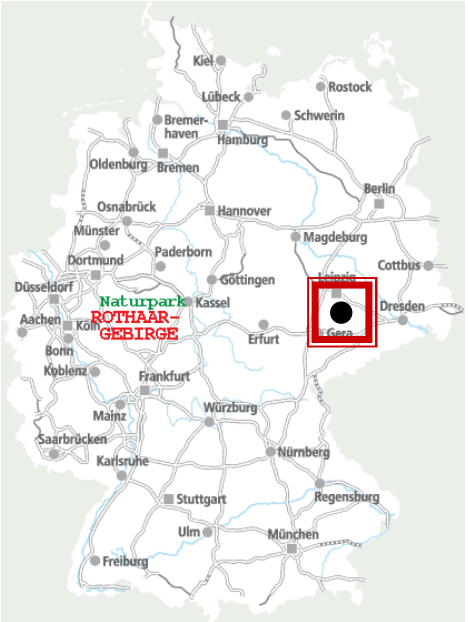
Bad Berleburg,
Wemlighausen

Bio-Systems



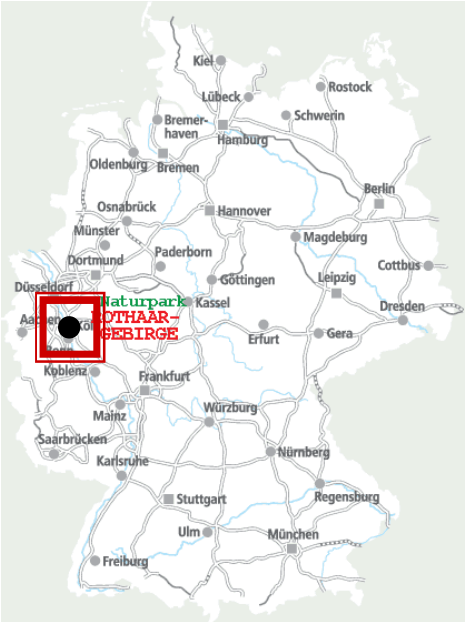
Bad Berleburg,
Wemlighausen

Bio-Systems



Bad Berleburg,
Wemlighausen

Bio-Systems

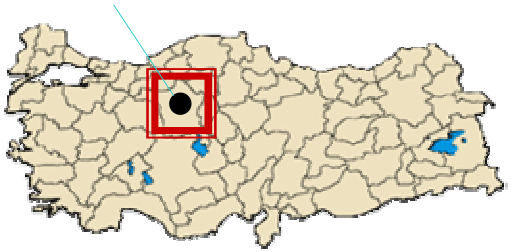


Bad Berleburg,
Wemlighausen

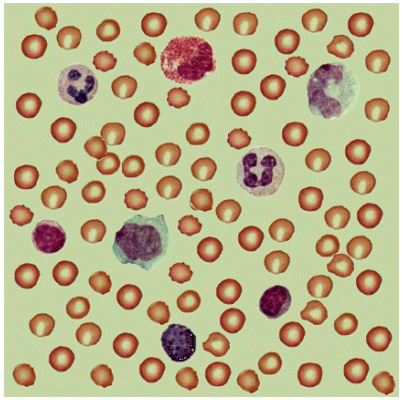
Bio-Systems

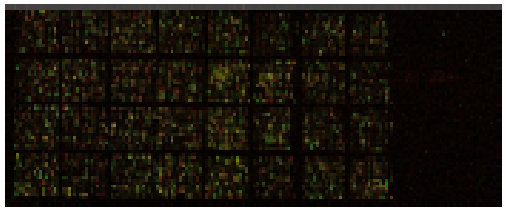
Bad Berleburg,
Wemlighausen

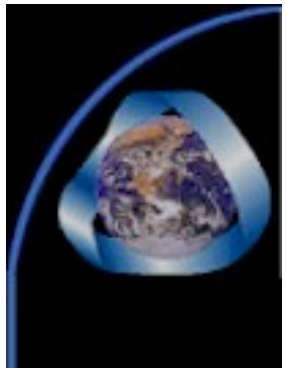
Ankara



Bio-Systems

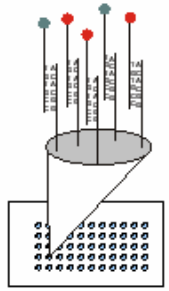


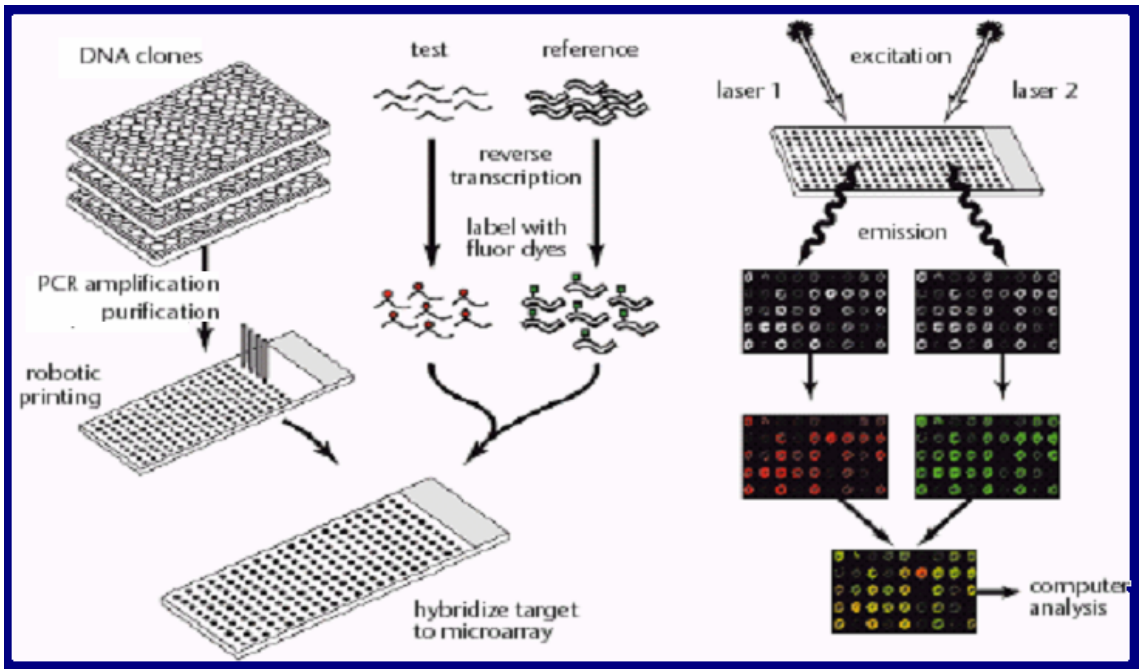




anticipation of gene patterns based on

DNA microarray chip experiments





M.U. Akhmet, H. Öktem
S.W. Pickl, E. Quek Ming Poh
T. Ergenç, B. Karasözen
J. Gebert, N. Radde, W.
Ö. U•ur, R. Wünschiers
M. Ta•tan, F.B. Y•lmaz

Gene Patterns Modeling & Prediction

least squares – ML

statistical learning

time-contin.

*E*xpression data

$$\dot{E} = M(E)\, E$$

$$E(0) = E_0$$

time-discr.

Ex.: Euler, Runge-Kutta

$$E_{k+1} = \mathrm{M}_k\, E_k$$

- $_k = (em_{ij}) \in$ M

Gene Patterns Model. & Pred.

For which parameters, i.e., for which set M (or: dynamics),
is stability guaranteed ?

development of process

its feasibility

goodness-of-fit (model) test

Def.: M is **stable** $:\Leftrightarrow$ $\exists$ B : (compl.) bounded neighbourhood of O_n,

$$\forall m \in \bullet\bullet \;,\; M_0, M_1, \ldots, M_{m-1} \in M :$$

$$(M_{m-1} M_{m-2} \ldots M_0) B \subseteq B .$$

Analysis with Polytopes

Theorem (Brayton, Tong 1979) :

Given a set $\mathrm{M} := \{ \mathrm{M}_0, \ldots, \mathrm{M}_{m-1} \}$ of m distinct complex matrices.

Then,

$$\mathrm{M} \text{ is stable } \Leftrightarrow B^* = \bigcup_{k=0}^{\infty} B_k \text{ is bounded .}$$

Here, B_0 is a bounded neighbourhood of 0_n ,

and for $k > 0$

$$B_k := \mathrm{H}\left(\bigcup_{i=0}^{\infty} \mathrm{M}_{k'}^{i} B_{k-1} \right),$$

where

$$k' := (k-1) \bmod m , \qquad \mathrm{H} : \text{ convex hull .}$$

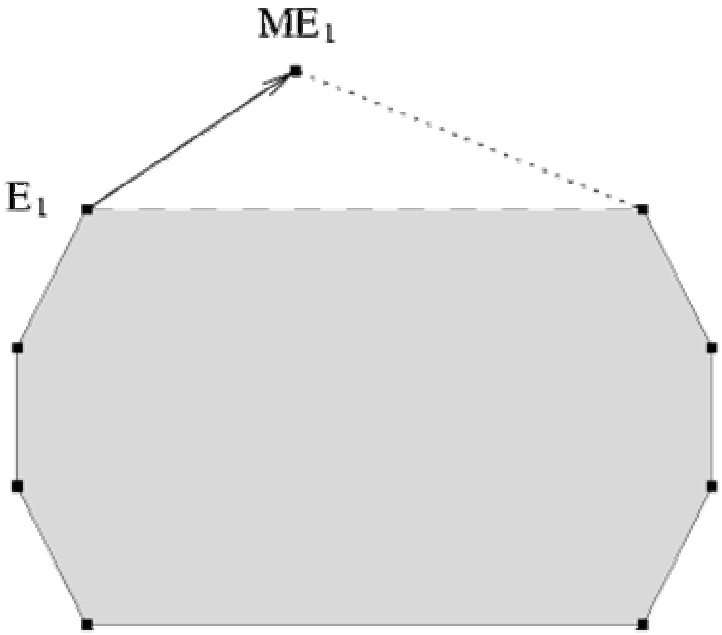
Extremal Points

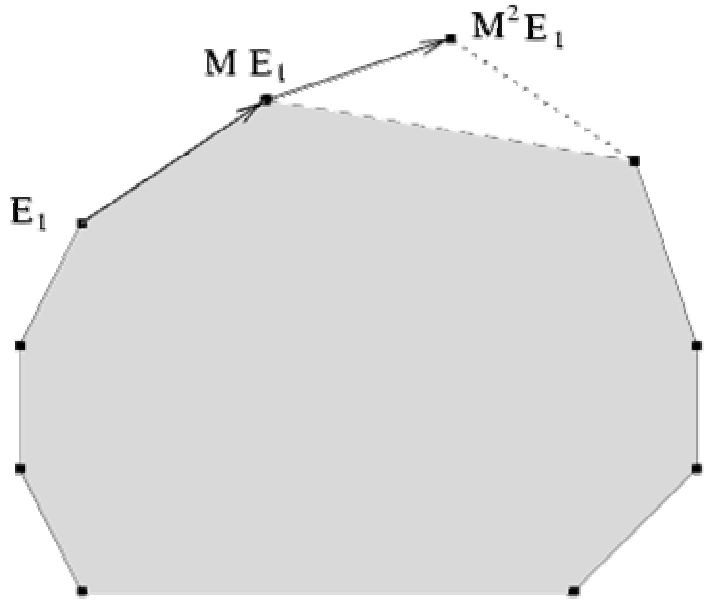
The "discrete" power of the algorithm is based on using **polyhedra** B_k and focussing on the **extremal points** of the sets B_k .

Theorem 1 : If z is an extremal point of B_k , then there exist $j \in \mathrm{IN}_0$ and an extremal point u of B_{k-1} , such that

$$z = M_{k'}^{j} u \ .$$

Construction Principle





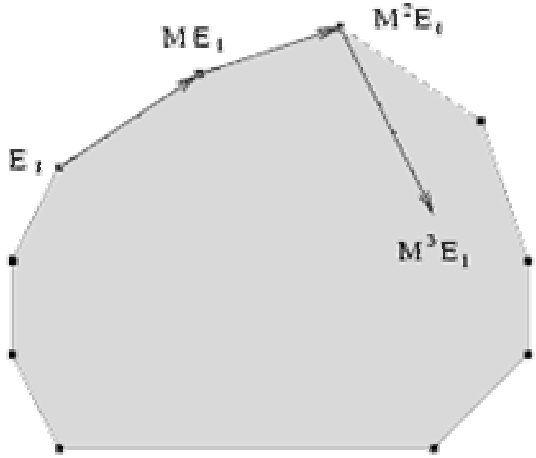
Stopping Criterion

Theorem 2 :

Let $z_i = \mathrm{M}_{k'}^{j}\, u_i$ (as above, $i \in \{1,2,\ldots,r\}$).

Then,

$$\mathrm{H}\,\{z_1,\ldots,z_r\} = B_k \quad \Leftrightarrow \quad \mathrm{M}_{k'} z_i \in \mathrm{H}\,\{z_1,\ldots,z_r\} \;\; \forall \;\; i = 1,2,\ldots,r.$$



Construction Principle

- $$B_k = B_{k_0} \quad (k \geq k_0) \quad \Rightarrow \begin{cases} \text{"}stopping\text{"} \ \ (at\ step\ k_0), \\ B^* = \bigcup_{i=0}^{\infty} B_i \quad bounded, \\ \text{stability}\ \ of\ \ matrices\,/\,dynamics \end{cases}$$

- $$\partial B_0 \cap \partial B_k = \emptyset \quad \Rightarrow \begin{cases} B^*\ \ unbounded \\ \text{in}stability \end{cases}$$

Gebert, Laetsch, Pickl, W., Wünschiers 2005

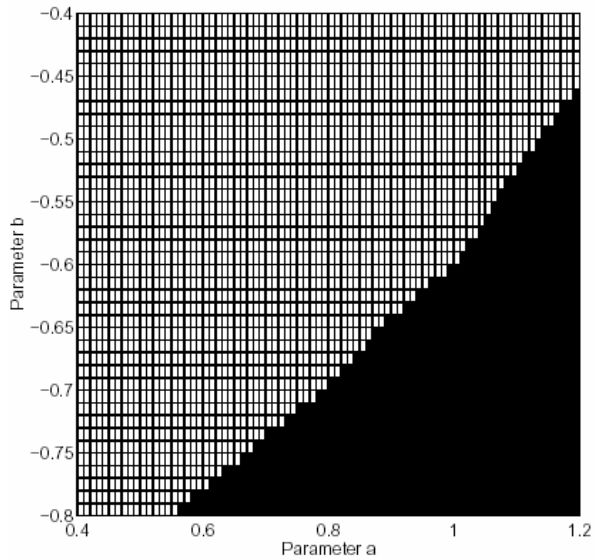
Ergenç, W. 2004

Numerical Example

Ex. (Pickl 1999) :

$$M = \{M_0, M_1\} \qquad M_0 = \begin{pmatrix} a & 1 \\ b & 0 \end{pmatrix}, \qquad M_1 = \begin{pmatrix} 0 & 1 \\ b & 0 \end{pmatrix}$$

algorithm



region of **stability**

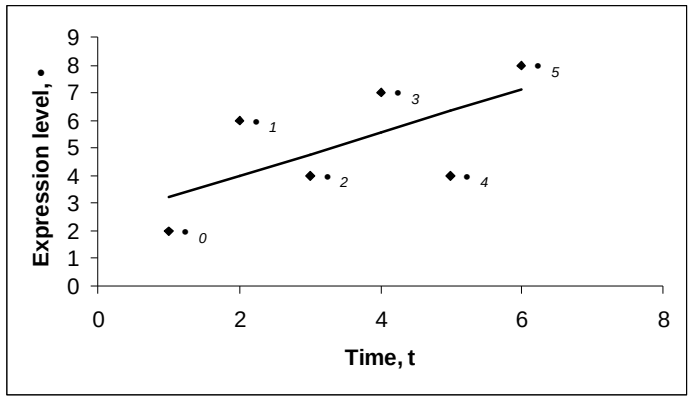
instability

Gene Network

Ex. :

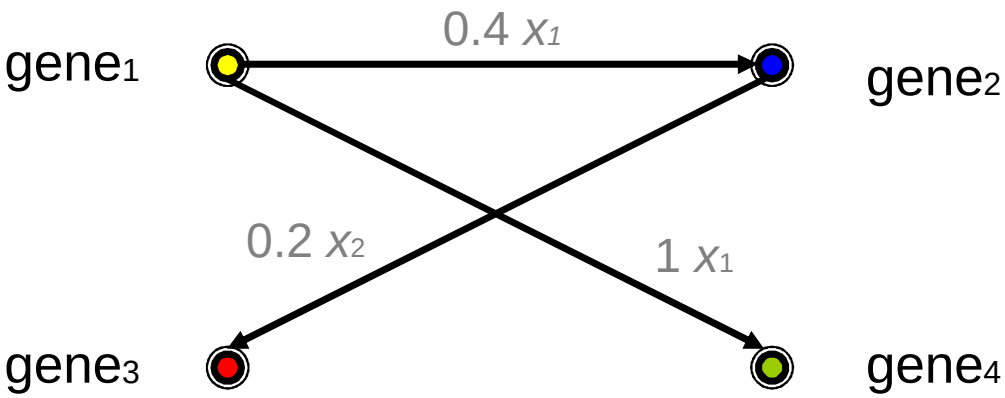
$$\dot{E} = M\ E \qquad h_k = 1$$

$$A = \begin{pmatrix} E_1(t_0) & E_2(t_0) & E_3(t_0) & E_4(t_0) \\ E_1(t_1) & E_2(t_1) & E_3(t_1) & E_4(t_1) \\ E_1(t_2) & E_2(t_2) & E_3(t_2) & E_4(t_2) \\ E_1(t_3) & E_2(t_3) & E_3(t_3) & E_4(t_3) \end{pmatrix} = \begin{pmatrix} 255 & 250 & 0 & 255 \\ 255 & 200 & 50 & 0 \\ 255 & 180 & 70 & 255 \\ 255 & 170 & 80 & 0 \end{pmatrix}$$



$$M = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0.4 & -0.61 & 0 & 0 \\ 0 & 0.2 & -0.39 & 0 \\ 1 & 0 & 0 & -2 \end{pmatrix}$$

Gene Network



F.B. Yilmaz 2004

$$\dot{E} = F(E)$$

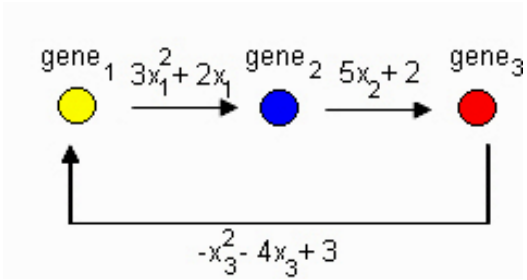
nonlinearities

Ex.: $$F_j(E) = \sum_{i=1}^{n} f_{j,i}(E_i) = \sum_{i=1}^{n} (a_{j,i}(E_i)^2 + b_{j,i}(E_i) + c_{j,i}).$$

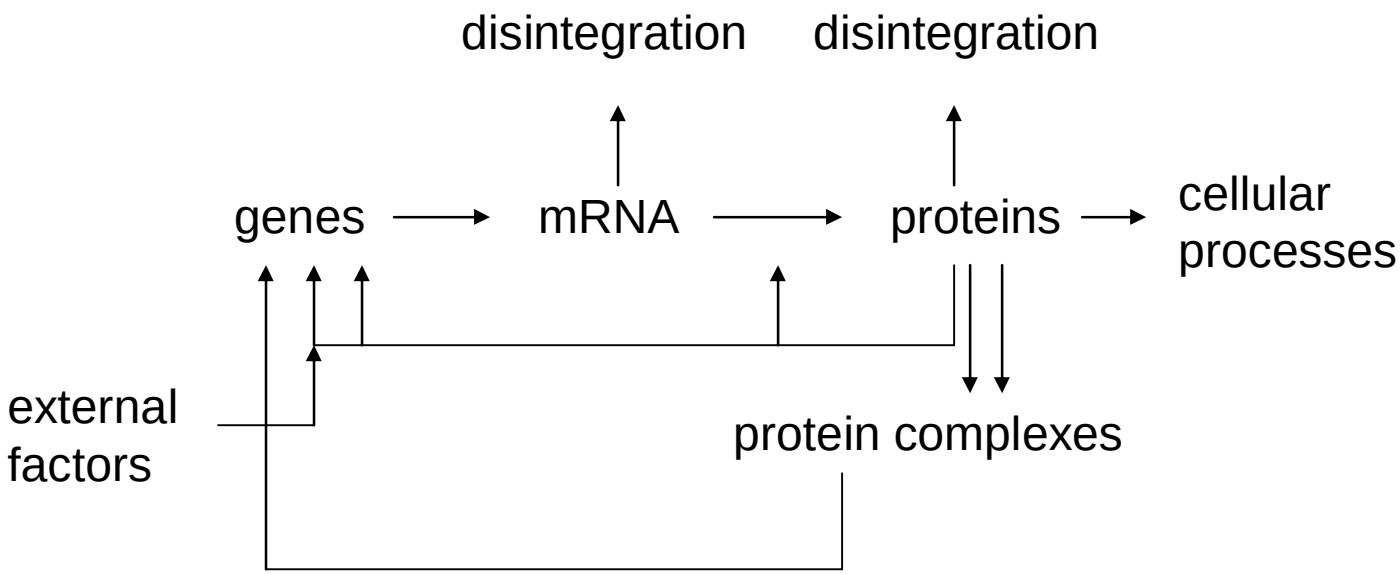
$\bar{E}_k$: exper. data

$\dot{\bar{E}}_k$: approx. increase/decrease

$$\min_{\substack{c_{j,1}, b_{j,1}, a_{j,1}, \\ \ldots \\ c_{j,n}, b_{j,n}, a_{j,n}}} \sum_{m=0}^{t-1} || F(\bar{E}_m) - \dot{\bar{E}}_m ||^2$$



Inference of Gene Regulatory Networks



Gene transcription also regulates the transcription factors defining a dynamic regulatory network involving highly *non*linear feedback mechanisms.

Proposed Model Class

piecewise linear:

$$E(k+1) = \mathrm{M}_{s(k)} E(k) + b_{s(k)}$$

$$s(k) = F_B Q(E(k-1))$$

$$Q_i(E(k)) = \begin{cases} 1 & \text{if } E_i(k) > \Omega_i \\ 0 & \text{else} \end{cases}$$

Akhmet, Gebert, Pickl, Öktem, W. 2004

Gebert, Radde, W. 2004

$$\dot{E}(t) = M_{s(t)} E(t) + b_{s(t)}$$

$$s(t) = F(Q(E(t), E(t-\mathrm{q}_1), \ldots, E(t-\mathrm{q}_p)))$$

$$Q_i(E^1, E^2, \ldots, E^{p+1}) \in \{0, 1, \ldots, q_i\}$$

Dynamics and Variation

- population dynamics

M.U. Akhmet , V. Tkachenko
H. Öktem, S.W. Pickl, W., et al.

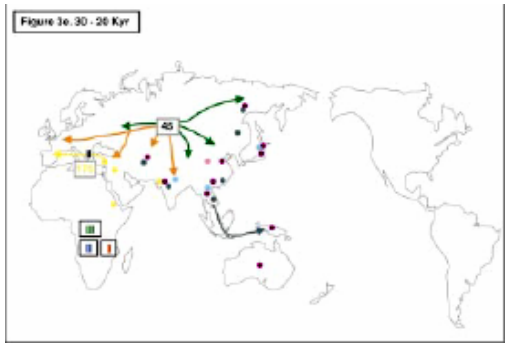
with delay and impulse

$$\dot{E}(t) = f(t, E(t), E([t+\tau]))$$

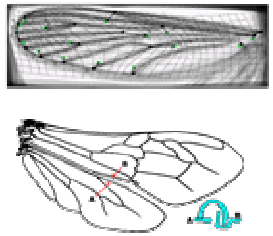
anticipation

- gene dyn. & variation

I. Togan
C. Berkman
et al.



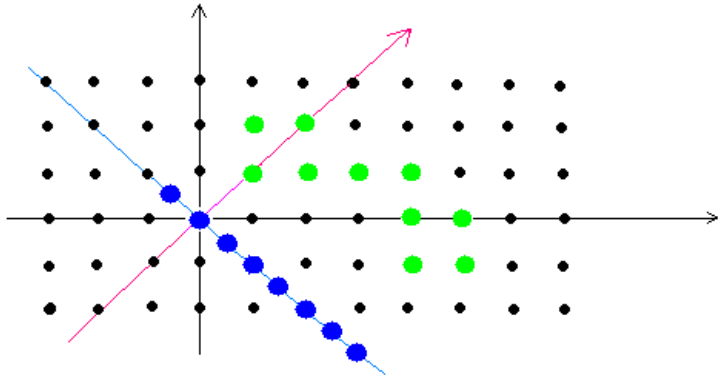
A. Kence
et al.



time

... Tomography

Discrete ...



Ö. Ya•ar, O. Özgür, W.

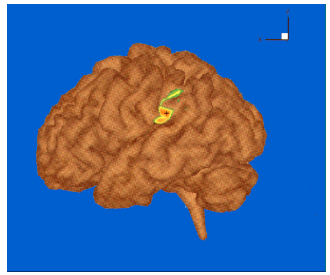
C. Diner, A. Do•an
F. Özbudak, A. Tiefenbach

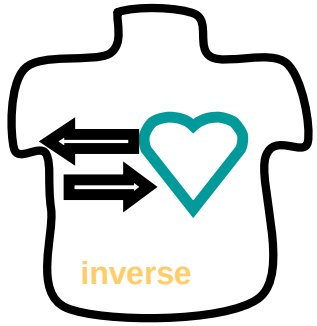
M. Eyübo•lu, N. Gençer
Y. Serina•o•lu, A. Kurt
S. Sar•kaya, W.

VLSI chip design

medicial imaging

Brain / Heart ...





inverse problems

Metabolic Engineering

sports (and general) medicine

math. modeling

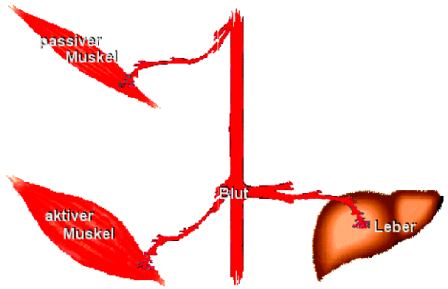
parameter estimation

object oriented

modules

DAE ODE

training program



A. Schulte Thomas 2004

S. Özö• ür 2005

Generalized Semi-Infinite Opt.

$$\mathcal{P}_{\mathcal{GSI}}(f,h,g,u,v) \quad \begin{cases} \text{Minimize} \quad f(x) \ \text{ on } \ M_{\mathcal{GSI}}[h,g], \quad \text{where} \\ M_{\mathcal{GSI}}[h,g] \ := \ \{\, x \in \mathbb{R}^n \mid \ h_i(x) = 0 \ \ (i \in I), \\ \qquad\qquad\qquad\qquad g(x,y) \geq 0 \ \ (y \in Y(x))\,\} \end{cases}$$

C^2

$$\begin{aligned} Y(x) \ &= \ M_{\mathcal{F}}[u(x,\cdot), v(x,\cdot)] \\ &:= \ \{\, y \in \mathbb{R}^q \mid \ u_k(x,y) = 0 \ \ (k \in K), \ \ v_\ell(x,y) \geq 0 \ \ (\ell \in L)\,\} \end{aligned}$$

I, K, L finite

W. 2003

Reverse Chebychev Approx.

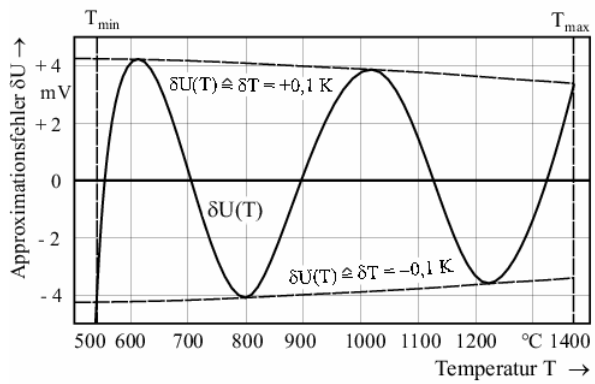
Ex.: approx. of a thermo-couple characteristic

Hoffmann, Reinhard

thermo-couple $f(y)$: *spline* of polynomials with deg. 3 – 13, on $[a,b]$

to be approx. by $\Psi(x_\circ, y) := \sum_{k=0}^{n^\circ} x_{k+1} y^k$:

- bounds on *error* $\delta(x_\circ, y) := \Psi(x_\circ, y) - f(y)$



Bernhard

$\mathcal{P}^1_{\mathcal{GSI}}$

(= *y*)

- some interpol.

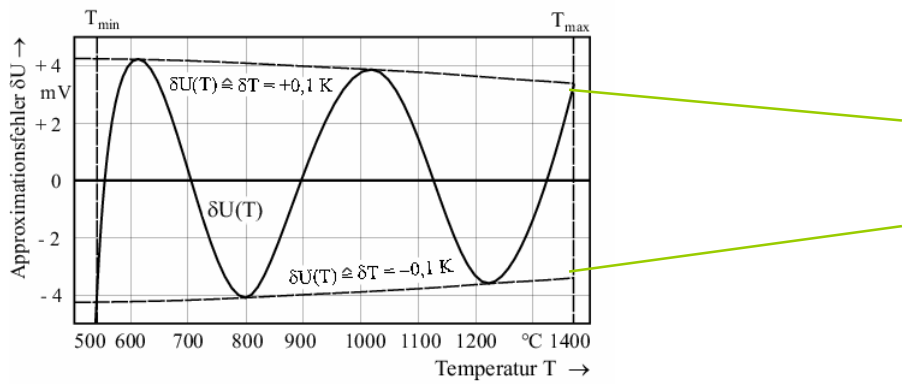
Reverse Chebychev Approx.

Ex.: approx. of a thermo-couple characteristic

thermo-couple $f(y)$: *spline* of polynomials with deg. 3 – 13, on $[a,b]$

to be approx. by $\Psi(x_\circ, y) := \sum_{k=0}^{n^\circ} x_{k+1} y^k$:

- bounds on *error* $\delta(x_\circ, y) := \Psi(x_\circ, y) - f(y)$



$\mathcal{P}^1_{\mathcal{GSI}}$

(= *y*)

- some interpol.

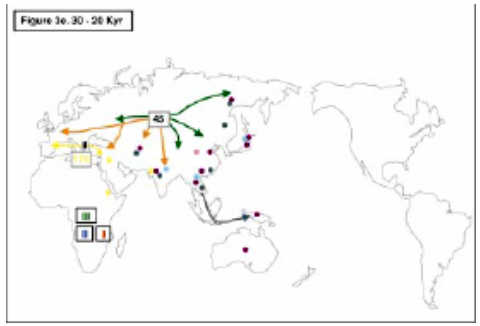
Reverse Chebychev Approx.

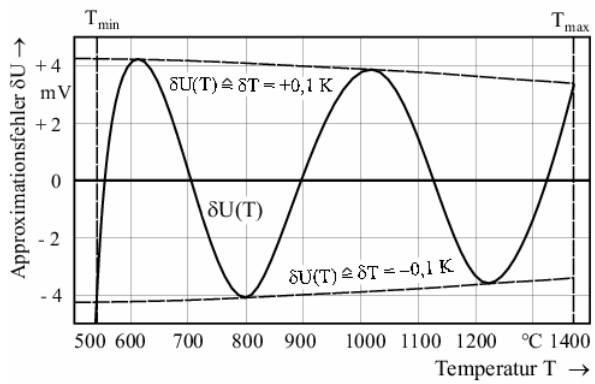
Ex.: approx. of a thermo-couple characteristic

thermo-couple $f(y)$: *spline* of polynomials with deg. 3 – 13, on $[a,b]$

to be approx. by $\Psi(x_o, y) := \sum_{k=0}^{n^o} x_{k+1} y^k$:

- bounds on *error* $\delta(x_o, y) := \Psi(x_o, y) - f(y)$





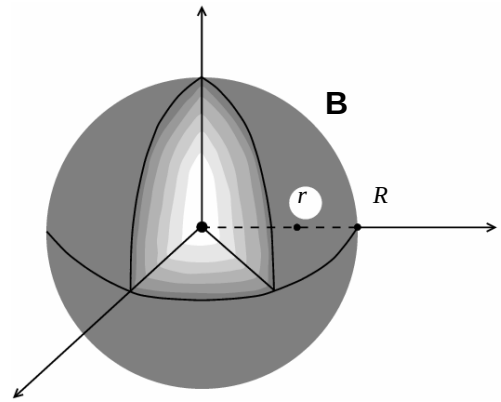
← time

(= *y*) →

- some interpol.

Time-Optimal Control

Ex.: time-*minimal* cooling (or heating) of



$$\mathcal{P}^{\mathsf{tm}} \quad \begin{cases} \text{Min} \quad \mathsf{I}(T,u) := T \quad \text{such that} \\ \text{there is a bounded function } \theta : [0,R] \times [0,\infty) \to I\!R, \text{ where} \\ \theta|(0,R] \times (0,\infty) \text{ is partially differentiable,} \\ u = \theta(R,\cdot)|[0,T] \text{ is continuous, and} \\ \theta_t(r,t) = a\Delta\theta(r,t) = \frac{a}{r^2}\frac{\partial}{\partial r}(r^2\theta_r(r,t)) \quad ((r,t) \in (0,R](0,\infty)), \\ \theta(r,0) = \theta_0 \quad (r \in [0,R]), \\ \theta(R,T) = \theta_E, \\ T \geq 0, \\ |\sigma_u(R,t)| \leq \sigma^* \quad (t \in [0,T]). \end{cases}$$

$$\mathcal{P}_T^{\mathsf{nm}} \quad \begin{cases} \text{Min}_{u_T} \; ||\sigma_{u_T}^{\theta_0}(R,\cdot)||_{\infty,T}, \\ \text{where } u_T \in C([0,T], I\!R) \text{ fulfills} \\ u_T(T) = \theta_E. \end{cases}$$

$\forall T > 0 \quad \exists! \; \hat{u}_T$

$\mathcal{P}^2_{\mathcal{GSI}}$

Anticipation

Ex.'s.:

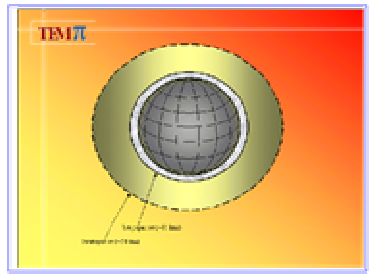
- **thermo**-regulation

- control of **earth warming**

Pickl, W.

$q(r,x,t)$

local-global



- *maximization* of time-horizon *longest* term approximation / description

anticipation

TEM Model

$$E_i(t+1) = E_i(t) + \sum_{j=1}^{n} em_{ij} M_j(t)$$

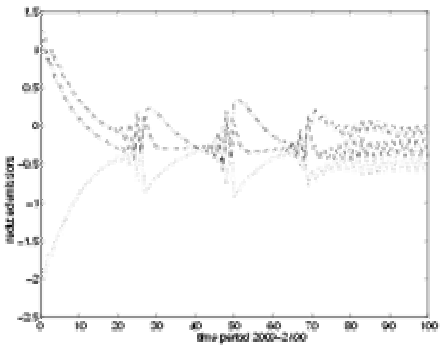
$$M_i(t+1) = M_i(t) - \lambda_i M_i(t)[M_i^* - M_i(t)] * [E_i(t) + \varphi_i \Delta E_i(t)] + u_i(t)$$

$u_i(t)$ control parameter

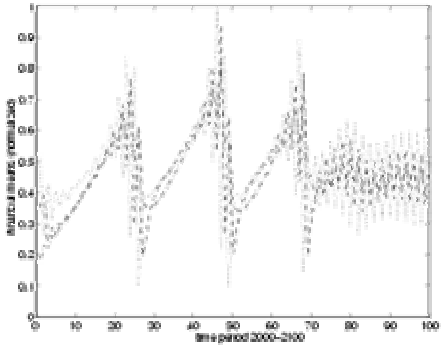
S.W. Pickl

Z. Alparslan

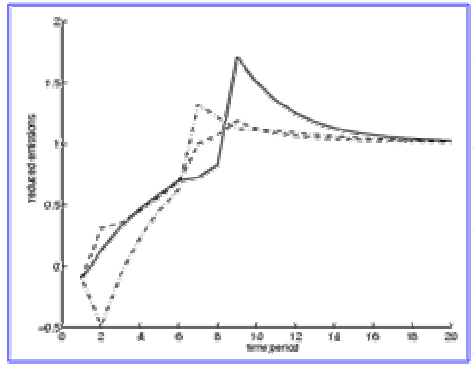
B. K., W.



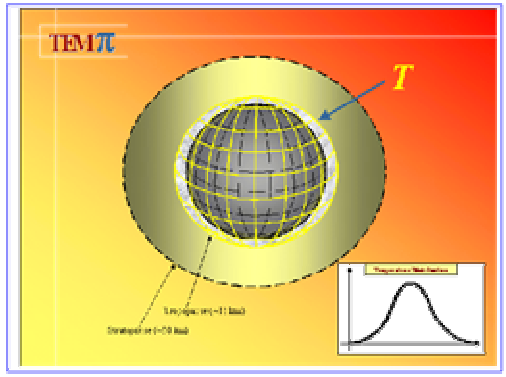
emissions reduced

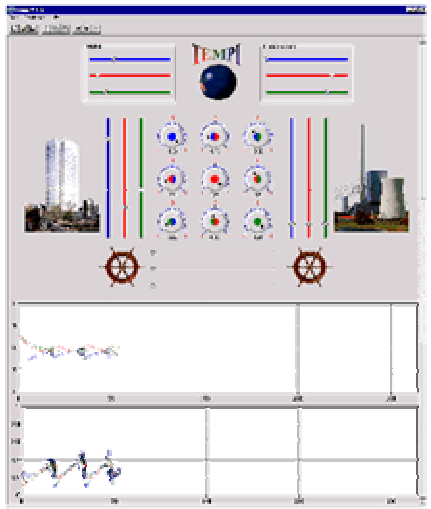


financial means



JET





EU project ***application***

"Joint International Emissions Trading,
Analysis,
Forecast,
and Optimal Strategies
in
Sustainable
Low Carbon Energy Management"

common learning

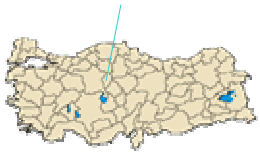
U. Leopold-W., B. K., S.W. P., M. Türkay, W.

Risk Management H. Körezlio• lu et al.

IAM, METU Ankara
CUBIC, Uni Cologne

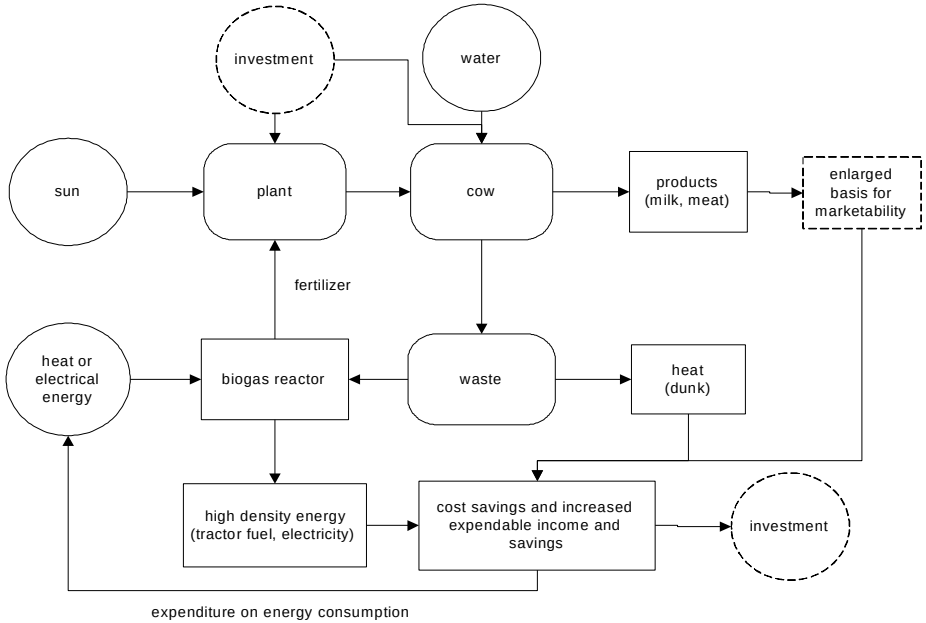
Sustainable Living

Balaban Valley



improvement of living conditions

learning



modeling

optimization

data mining

D. DeTombe, A., I., H. Gökmen

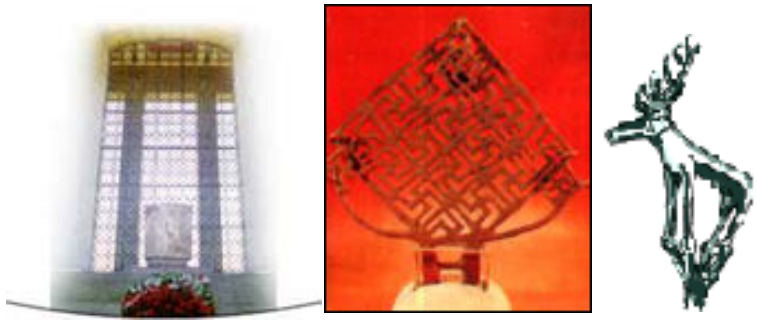
S. Kayal•• il, M., Y. Ecevit

T. Bali, W. et al.

Turkey

METU

Ankara



Turkey

Conclusions and Perspectives

Operations Research Society

of Israel

Operations Research Society

of Hungary

Association of European

Operational Research Societies

Operations Research

Society of Turkey

EURO Working Group

on Continuous Optimization

Operations Research Society

of Germany

Conclusions and Perspectives

5th ***EUROPT Workshop***

"Advances in

Continuous Optimization"

Reykjavik, Iceland

June 29 – July 1, 2006

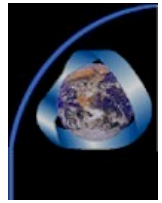
EURO Summer Institute

"Optimization Challenges in Engineering: Methods, Software, and Applications"

Wittenberg, Germany
August 18 – September 2, 2006

OR for Better Management of Sustainable Development

***EURO XXI* in Iceland**
July 2-5, 2006



Earth Institute

21st European Conference on Operational Research

Young People for OR in Developing Countries

Balaban Valley Project

IAM, METU Ankara
CUBIC, Uni Cologne

Sincere invitation

...

to **EUROPT**

EURO Working Group

in Continuous Optimization

http://www.iam.metu.edu.tr/EUROPT/

two new EURO WGs planned:

Computational Biology & Bioinformatics

OR for Development

and ***Computational Biology and Medicine Group***

http://www.iam.metu.edu.tr/research/groups/compbio/index.html

gweber@metu.edu.tr