

Multi-scale modeling of biological systems using structured hybrid models

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11.04.2009



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Agenda

- the challenges of predictive modelling in biology
- hybrid models – the integration concept
- Example: integration of clinical and –omics data
- summary

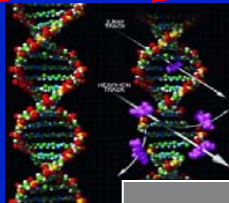
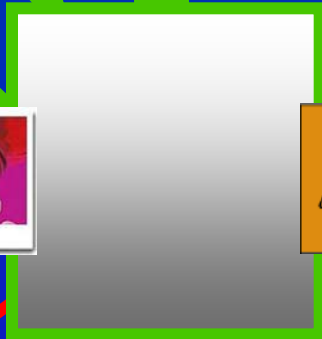
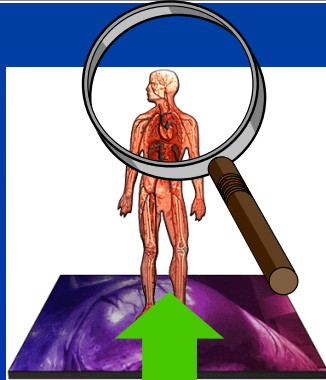
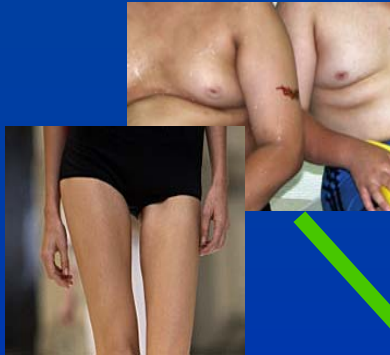


Gene	Expression	Protein	Activity	Pathway	Cell Type	Condition	Time	Location	Notes
BRCA1	0.12	0.05	0.01	Cell Cycle	Epithelial	Normal	0h	Nucleus	Baseline
BRCA1	0.15	0.06	0.02	Cell Cycle	Epithelial	Normal	2h	Nucleus	Stimulated
BRCA1	0.18	0.07	0.03	Cell Cycle	Epithelial	Normal	4h	Nucleus	Stimulated
BRCA1	0.21	0.08	0.04	Cell Cycle	Epithelial	Normal	6h	Nucleus	Stimulated
BRCA1	0.24	0.09	0.05	Cell Cycle	Epithelial	Normal	8h	Nucleus	Stimulated
BRCA1	0.27	0.10	0.06	Cell Cycle	Epithelial	Normal	10h	Nucleus	Stimulated
BRCA1	0.30	0.11	0.07	Cell Cycle	Epithelial	Normal	12h	Nucleus	Stimulated
BRCA1	0.33	0.12	0.08	Cell Cycle	Epithelial	Normal	14h	Nucleus	Stimulated
BRCA1	0.36	0.13	0.09	Cell Cycle	Epithelial	Normal	16h	Nucleus	Stimulated
BRCA1	0.39	0.14	0.10	Cell Cycle	Epithelial	Normal	18h	Nucleus	Stimulated
BRCA1	0.42	0.15	0.11	Cell Cycle	Epithelial	Normal	20h	Nucleus	Stimulated
BRCA1	0.45	0.16	0.12	Cell Cycle	Epithelial	Normal	22h	Nucleus	Stimulated
BRCA1	0.48	0.17	0.13	Cell Cycle	Epithelial	Normal	24h	Nucleus	Stimulated
BRCA1	0.51	0.18	0.14	Cell Cycle	Epithelial	Normal	26h	Nucleus	Stimulated
BRCA1	0.54	0.19	0.15	Cell Cycle	Epithelial	Normal	28h	Nucleus	Stimulated
BRCA1	0.57	0.20	0.16	Cell Cycle	Epithelial	Normal	30h	Nucleus	Stimulated
BRCA1	0.60	0.21	0.17	Cell Cycle	Epithelial	Normal	32h	Nucleus	Stimulated
BRCA1	0.63	0.22	0.18	Cell Cycle	Epithelial	Normal	34h	Nucleus	Stimulated
BRCA1	0.66	0.23	0.19	Cell Cycle	Epithelial	Normal	36h	Nucleus	Stimulated
BRCA1	0.69	0.24	0.20	Cell Cycle	Epithelial	Normal	38h	Nucleus	Stimulated
BRCA1	0.72	0.25	0.21	Cell Cycle	Epithelial	Normal	40h	Nucleus	Stimulated
BRCA1	0.75	0.26	0.22	Cell Cycle	Epithelial	Normal	42h	Nucleus	Stimulated
BRCA1	0.78	0.27	0.23	Cell Cycle	Epithelial	Normal	44h	Nucleus	Stimulated
BRCA1	0.81	0.28	0.24	Cell Cycle	Epithelial	Normal	46h	Nucleus	Stimulated
BRCA1	0.84	0.29	0.25	Cell Cycle	Epithelial	Normal	48h	Nucleus	Stimulated
BRCA1	0.87	0.30	0.26	Cell Cycle	Epithelial	Normal	50h	Nucleus	Stimulated
BRCA1	0.90	0.31	0.27	Cell Cycle	Epithelial	Normal	52h	Nucleus	Stimulated
BRCA1	0.93	0.32	0.28	Cell Cycle	Epithelial	Normal	54h	Nucleus	Stimulated
BRCA1	0.96	0.33	0.29	Cell Cycle	Epithelial	Normal	56h	Nucleus	Stimulated
BRCA1	0.99	0.34	0.30	Cell Cycle	Epithelial	Normal	58h	Nucleus	Stimulated
BRCA1	1.02	0.35	0.31	Cell Cycle	Epithelial	Normal	60h	Nucleus	Stimulated
BRCA1	1.05	0.36	0.32	Cell Cycle	Epithelial	Normal	62h	Nucleus	Stimulated
BRCA1	1.08	0.37	0.33	Cell Cycle	Epithelial	Normal	64h	Nucleus	Stimulated
BRCA1	1.11	0.38	0.34	Cell Cycle	Epithelial	Normal	66h	Nucleus	Stimulated
BRCA1	1.14	0.39	0.35	Cell Cycle	Epithelial	Normal	68h	Nucleus	Stimulated
BRCA1	1.17	0.40	0.36	Cell Cycle	Epithelial	Normal	70h	Nucleus	Stimulated
BRCA1	1.20	0.41	0.37	Cell Cycle	Epithelial	Normal	72h	Nucleus	Stimulated
BRCA1	1.23	0.42	0.38	Cell Cycle	Epithelial	Normal	74h	Nucleus	Stimulated
BRCA1	1.26	0.43	0.39	Cell Cycle	Epithelial	Normal	76h	Nucleus	Stimulated
BRCA1	1.29	0.44	0.40	Cell Cycle	Epithelial	Normal	78h	Nucleus	Stimulated
BRCA1	1.32	0.45	0.41	Cell Cycle	Epithelial	Normal	80h	Nucleus	Stimulated
BRCA1	1.35	0.46	0.42	Cell Cycle	Epithelial	Normal	82h	Nucleus	Stimulated
BRCA1	1.38	0.47	0.43	Cell Cycle	Epithelial	Normal	84h	Nucleus	Stimulated
BRCA1	1.41	0.48	0.44	Cell Cycle	Epithelial	Normal	86h	Nucleus	Stimulated
BRCA1	1.44	0.49	0.45	Cell Cycle	Epithelial	Normal	88h	Nucleus	Stimulated
BRCA1	1.47	0.50	0.46	Cell Cycle	Epithelial	Normal	90h	Nucleus	Stimulated
BRCA1	1.50	0.51	0.47	Cell Cycle	Epithelial	Normal	92h	Nucleus	Stimulated
BRCA1	1.53	0.52	0.48	Cell Cycle	Epithelial	Normal	94h	Nucleus	Stimulated
BRCA1	1.56	0.53	0.49	Cell Cycle	Epithelial	Normal	96h	Nucleus	Stimulated
BRCA1	1.59	0.54	0.50	Cell Cycle	Epithelial	Normal	98h	Nucleus	Stimulated
BRCA1	1.62	0.55	0.51	Cell Cycle	Epithelial	Normal	100h	Nucleus	Stimulated

Predictive modelling in biology: the challenge of scales and diversity



Medical Therapy and Diagnostics



Genome / Proteome

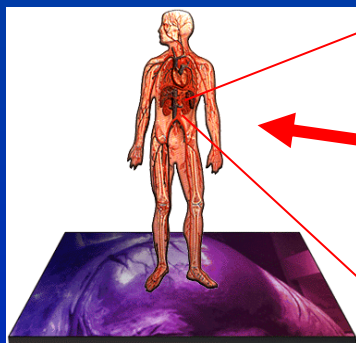
Technology Services

The challenge of predictive modelling in biology

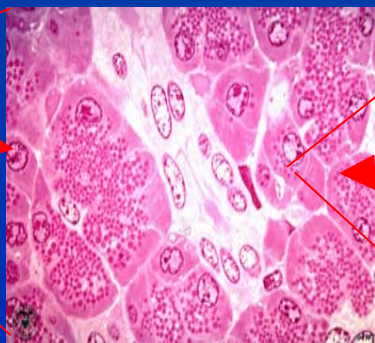
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2.) lacking data

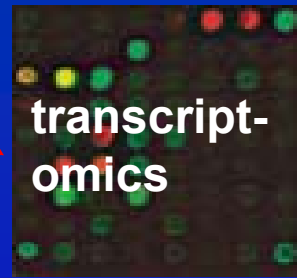
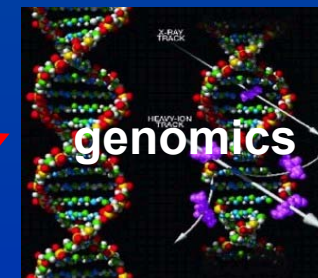
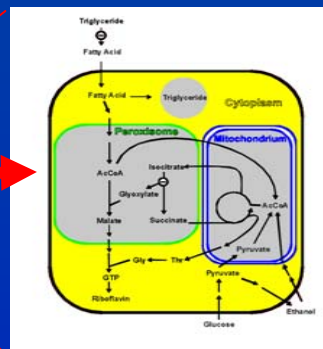
clinics



cell biology



metabolomics
proteomics

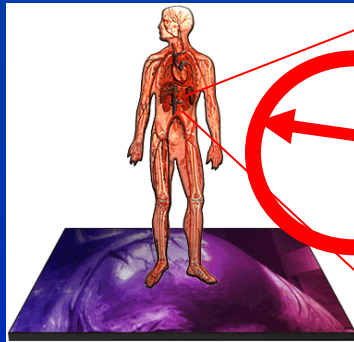


**we will never have all parameters
for all components in a biological system...**

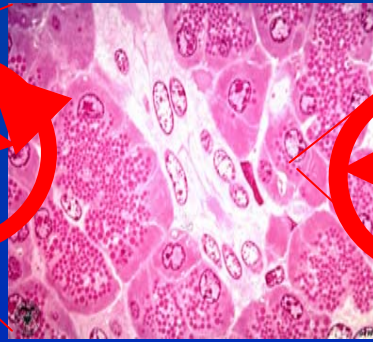
The challenge of predictive modelling in biology

2.) lacking data

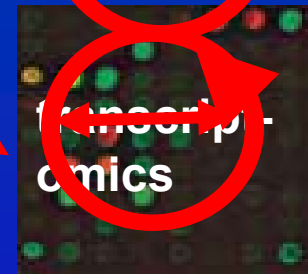
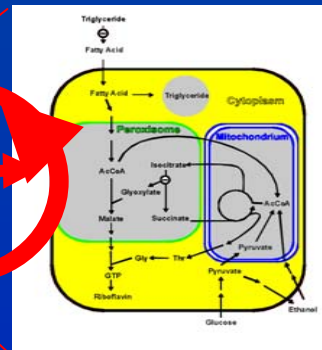
clinics



cell biology



metabolomics
proteomics



... but the components are mutually coupled by closed-loop regulation circuits

- ⇒ the true dimensionality of biology is much smaller than # of components
- ⇒ the strong mutual coupling leads to extremely complex, unknown coregulation structures

The challenge of predictive modelling in biology

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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Therefore

... which requires maths adapted to the structures of biological co-regulation

ating

- **genotype**

AC(A) TG
TG (T) AC

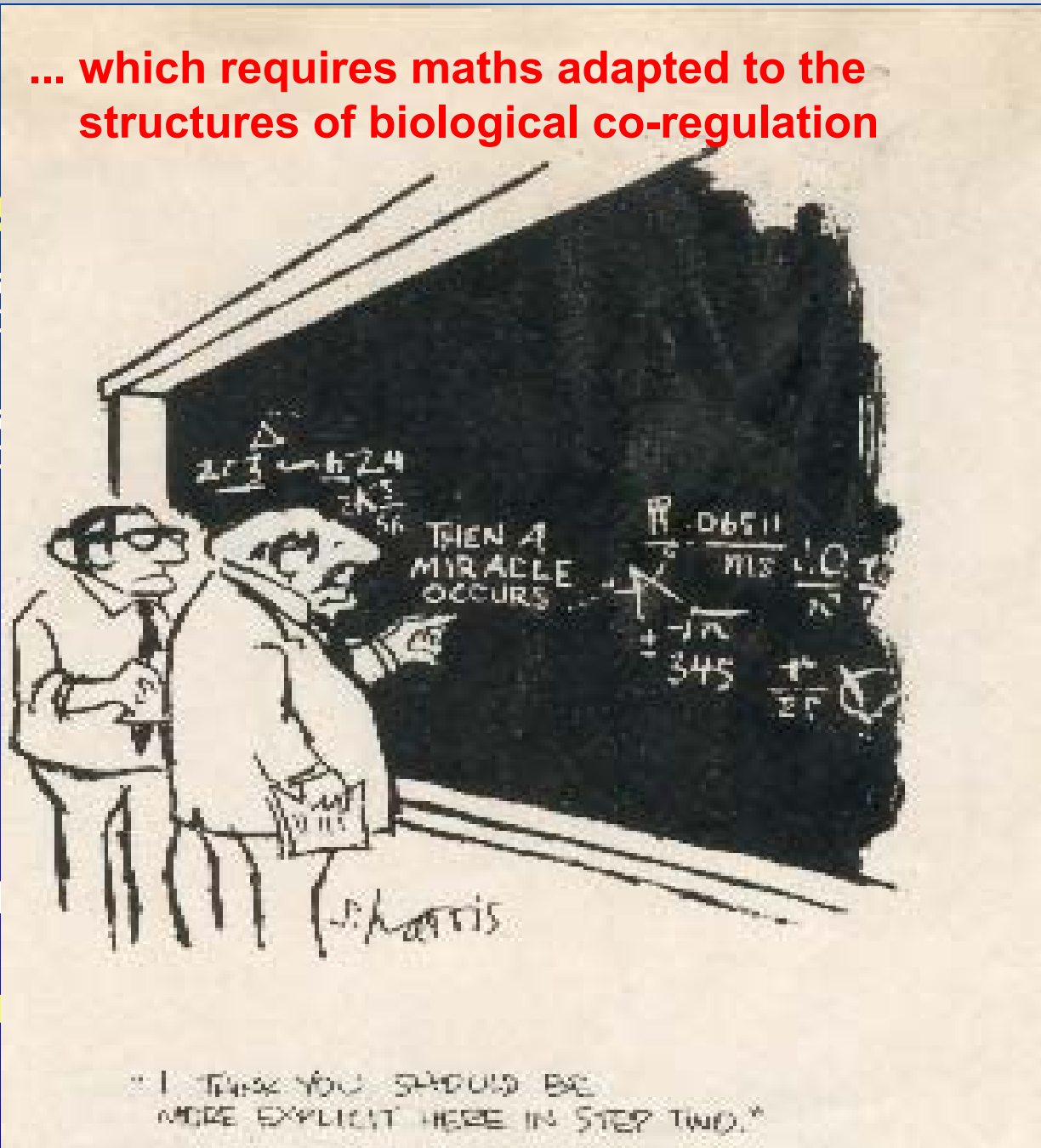
AC(A) TG
TG (T) AC

- **gene e**

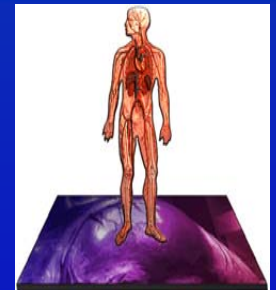
Microar
data

physiolog

- **releva**



Phenotype



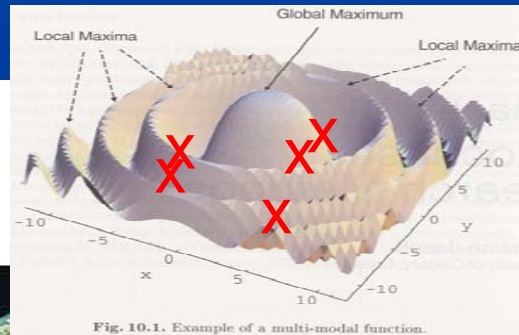
Technology Services

Agenda

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- hybrid models – the integration concept
- Example: integration of clinical and –omics data
- summary



the two extremes of modeling technology

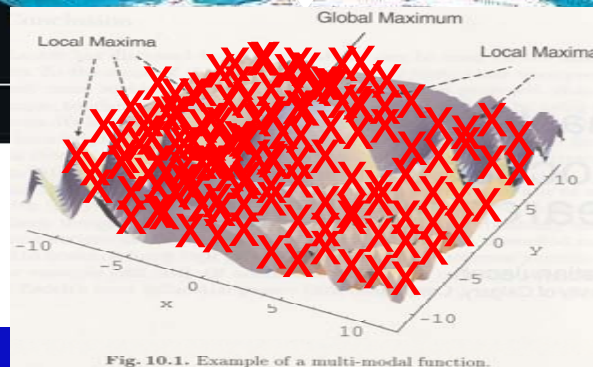


mechanistic models :

- detailed knowledge



is there a smooth transition
in modeling technology?



black box models :

- high data demand

- no extrapolation



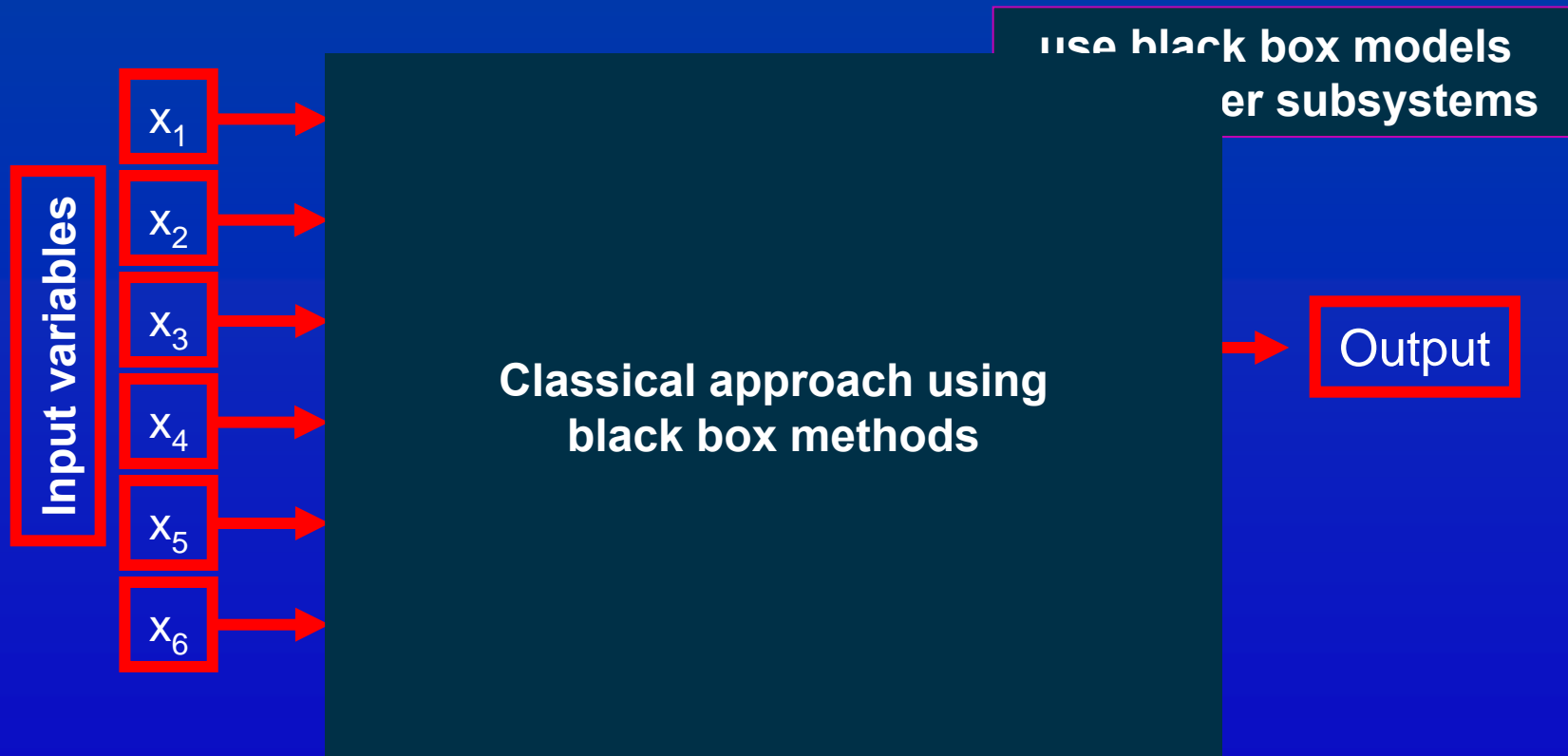
how to realize SHM



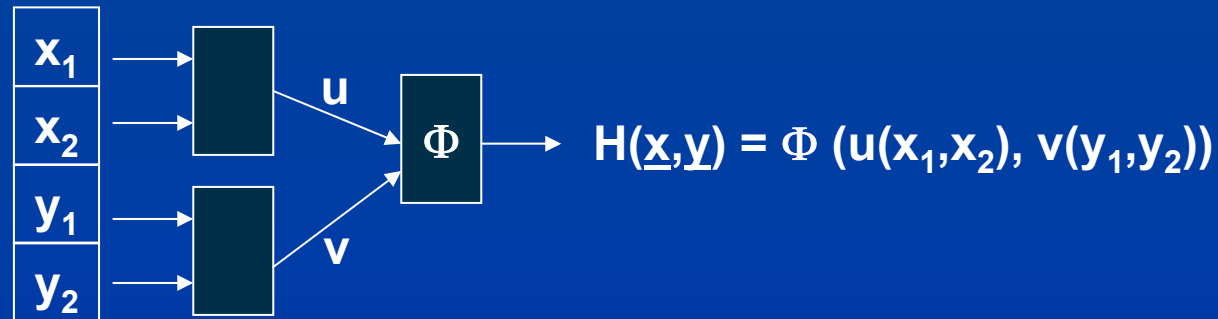
Use a priori knowledge of system structure S

black box model → **functional network model (SHM)**:

- Functional subsystems \leftrightarrow nodes
- interactions between the subsystems \leftrightarrow edges



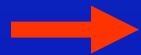
use mechanistic models where established Technology Services



$$\partial_{\underline{y}} \frac{\partial \underline{x}_1 \mathbf{H}}{\partial \underline{x}_2 \mathbf{H}} = \partial_{\underline{y}} \frac{\cancel{\Phi_{,1}} \partial \underline{x}_1 \mathbf{u}}{\cancel{\Phi_{,1}} \partial \underline{x}_2 \mathbf{u}} = 0$$

“structure constraint equations“ in form of PDE’s:

$$\partial_{y_i} \partial x_1 \mathbf{H} \partial x_2 \mathbf{H} - \partial_{y_i} \partial x_2 \mathbf{H} \partial x_1 \mathbf{H} = 0 \quad \text{for } i = 1, 2$$



$$\partial x_i \partial y_1 \mathbf{H} \partial y_2 \mathbf{H} - \partial x_i \partial y_2 \mathbf{H} \partial y_1 \mathbf{H} = 0 \quad \text{for } i = 1, 2$$



**The model can be identified
if the data guarantee the well-posedness
of the initial value problem**



Results:

- For **tree structures** :

complexity = \max_S (number of input nodes in any bb - node in S)

Schuppert 1999, B. Fiedler & Schuppert (IMA Journal of appl. Maths, 2008)

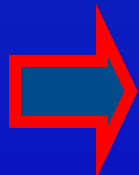
- S can be directly **re-engineered from large data sets**
(eg. from high throughput screening)

Schuppert 2001, European Patent

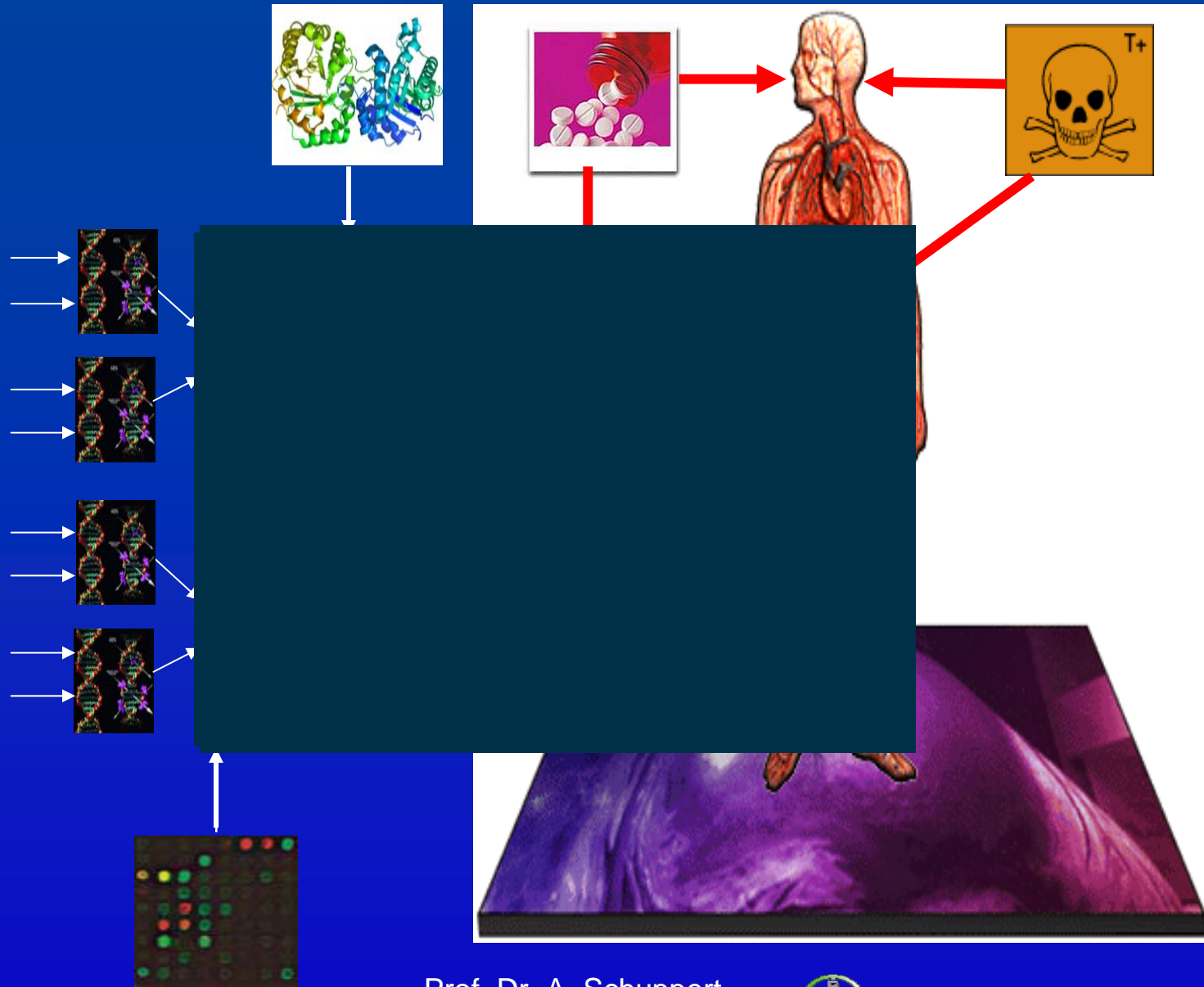
+ functional networks reduce model complexity by orders of magnitude which can be quantified

+ optimal choice between investment into data and science can be realized

+ network reengineering of functional networks is possible from HTS data



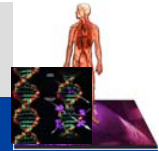
Hybrid modeling: combination of mechanistic and black box models



Agenda

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- **Example: integration of clinical and –omics data**
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Challenge : Prediction of ADR, e.g. rhabdomyolysis
(strongly increased CK - level) caused by statin therapy

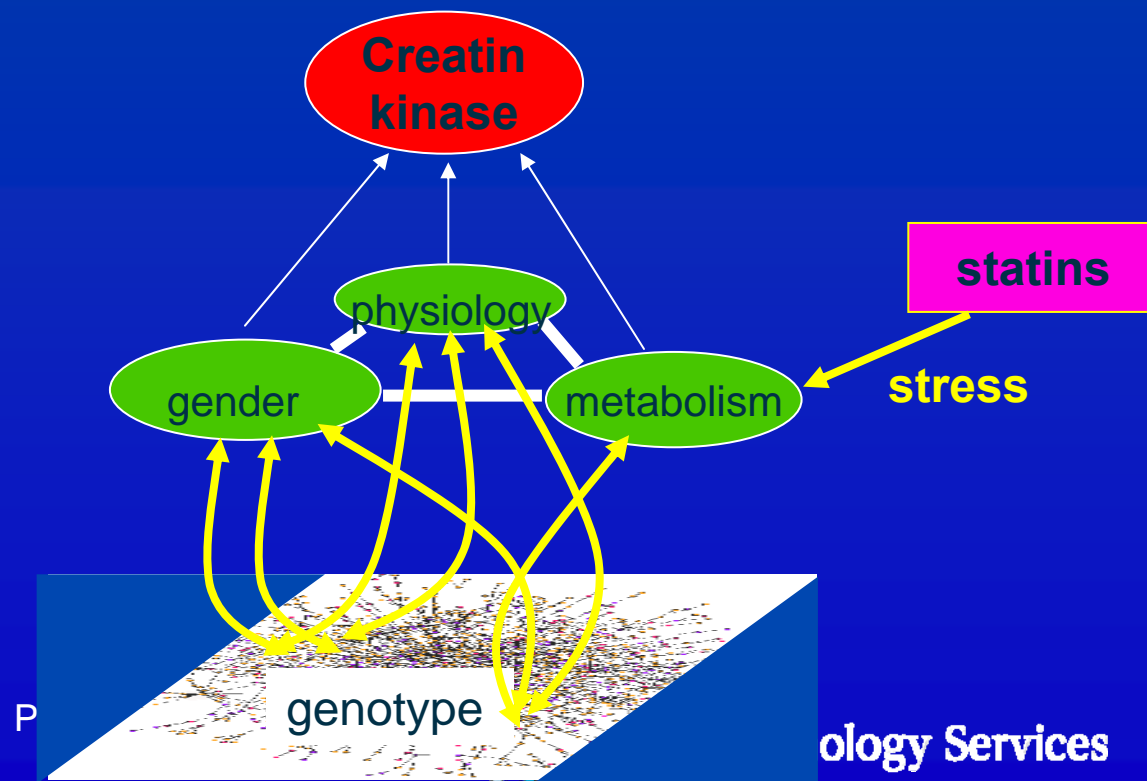
- Data:
- > 3000 SNP's on 86 genes
 - clinical parameters
 - 312 patients

Goal: Identify

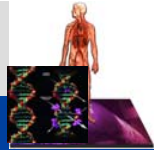
$$[CK] = F(\text{genotype}, \dots)$$

Problem:

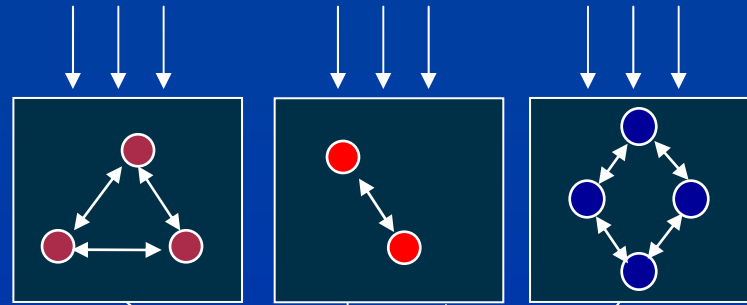
standard approaches failed,
because of
huge network complexity



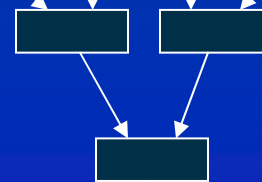
functional network model for statin-induced CK increase



clinical data

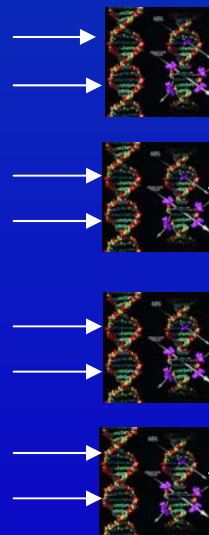


unsupervised patient stratification



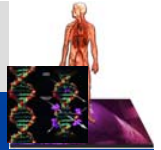
physiology-based CK-prediction model

integration of genotype data



to predict phenotype





Results:

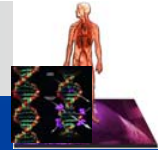
1. Genotype-based ADR-prediction does not meet accuracy aims

	standard biomarker	network biomarker
	genotype only and black box	clinical parameters and genotype
specificity (aim >98%)	70%	97,7%
sensitivity (aim >80%)	70%	90,1%

2. Integration of clinical and genotype data proved to be superior to the classical methods



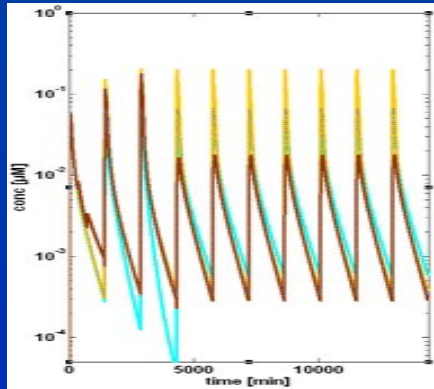
hybrid model for statin therapy (BMBF HEPATOSYS)



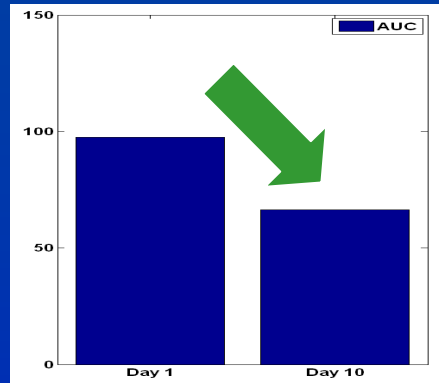
PBPK models with dynamics of gene expression allow to model different AUC and C_{max} adaptation per statin...

Pravastatin

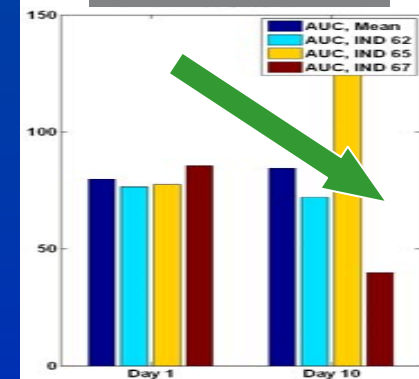
Concentration profiles



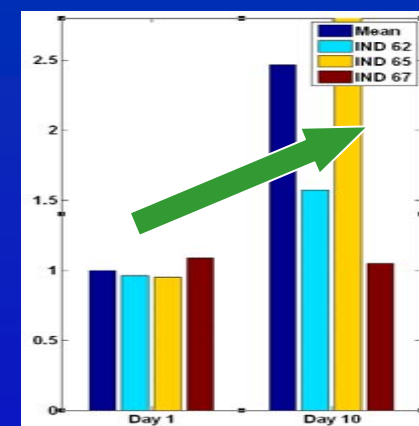
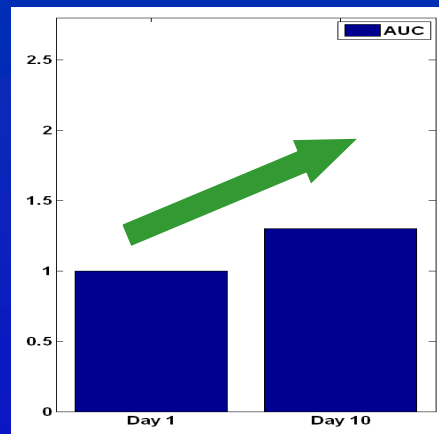
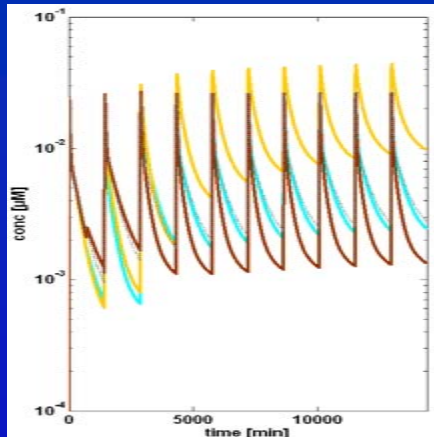
Literature data



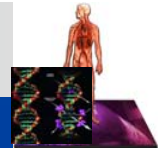
comb. PBPK simulation



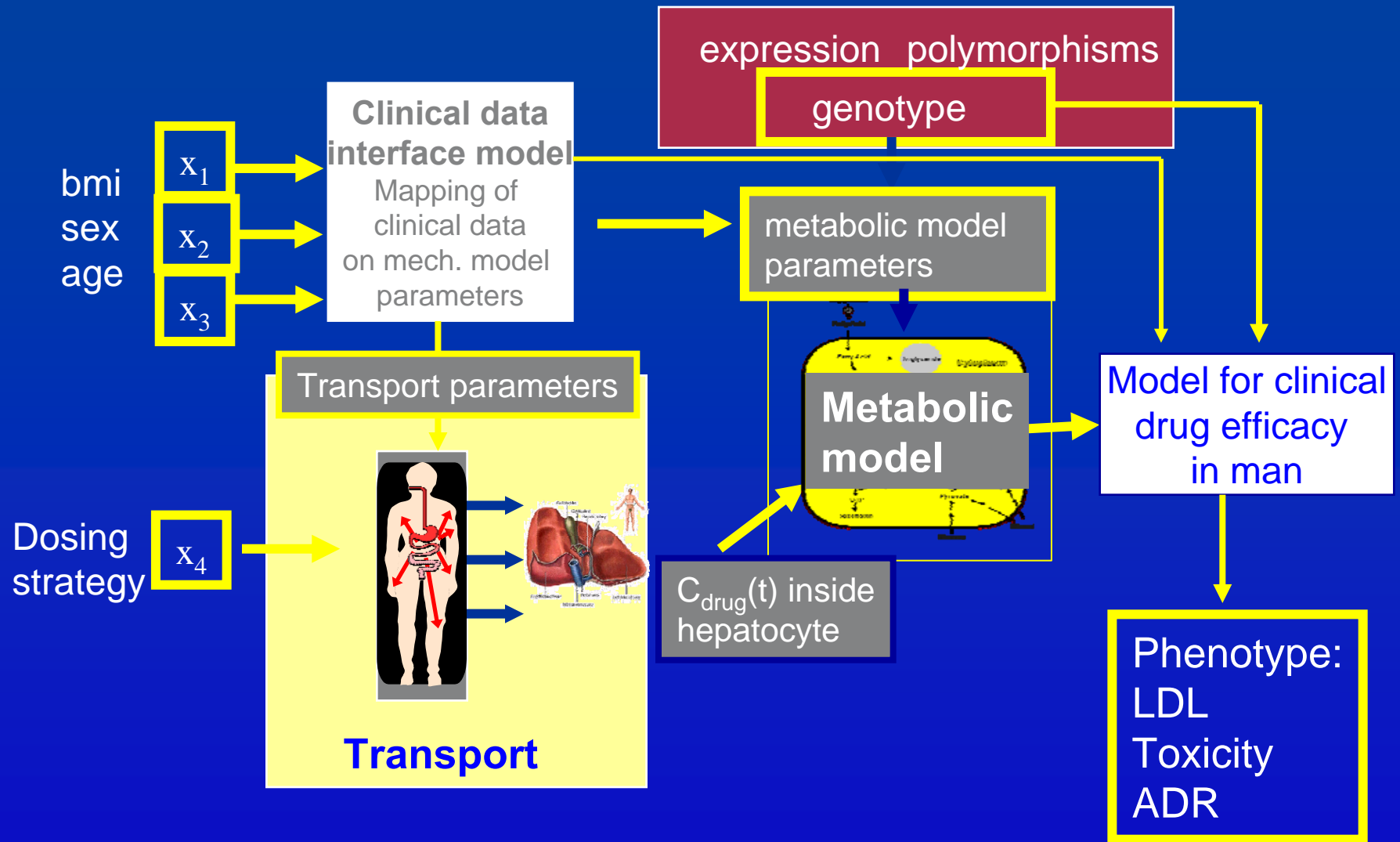
Atorvastatin



...but patient specific variations require a multi-scale approach



hybrid model for statin therapy

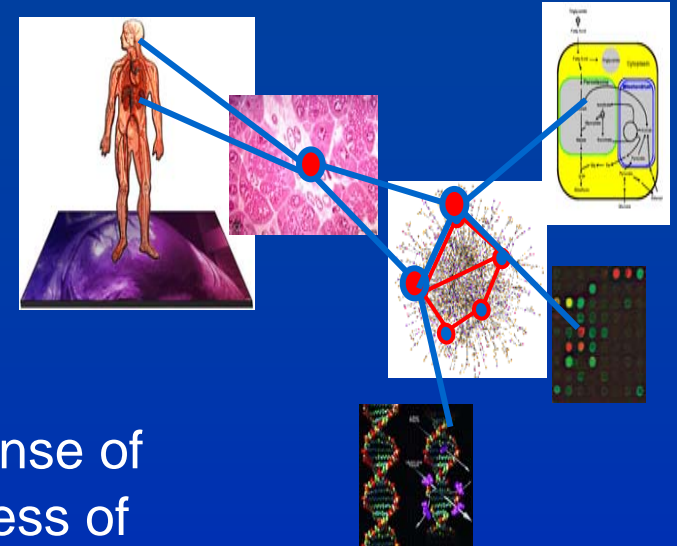


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Summary



- modelling slow processes involving stress response of biological regulation networks is crucial for success of systems biology in drug R&D and personalized medicine
- this task is hampered by the huge complexity of the networks in time scales, regulation hierarchy and closed loop control
- structured hybrid modelling using functional networks provides sufficient tools to establish a bridge between purely (hopefully) predictive and deductive mechanistic models