

Live patterns through creativity and selection:
the art of systems biology

Manchester Centre for Integrative Systems Biology
Manchester Doctoral Training Centre Systems Biology
Netherlands Institute for Systems Biology

20101110

Systems Biology: the Arts of Biology

- Systems Biology: why?
- Systems Biology: what?
- Examples:
 - Pattern formation
 - Simpler than complexity; more complex than simple
 - Robustness
 - Differential network-based drug targeting
 - The silicon/virtual human

Westerhoff et al., London 20101110

The human genome sequence...: we have all the components

- 12 068 kbp, a few transcriptomes, an interactome (?), parts of the metabolome further and

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ATGCGCATCGATGCGCATCGCGCGTAGCT
TACGGCTAGCTACGGCTAGCGCGCATCGA
UACGCGUAGCUAAGC

We (can) know 'everything'

ATP

Westerhoff et al., London 20101110

but can we now cure our diseases?

Or has it led to a Babylonian language/data confusion?

Brueghel

NISB


every new publication

we of the

NISB

MANCHESTER 1924

A problem such as that of Margritte




Ceci n'est pas une pipe.

We can see all the pixels of the pipe, but this is not the essence of the pipe itself: It is a lifeless image

Westerhoff et al., London 20101110

MANCHESTER 1924

Then we'd rather have a less precise image that conveys more of the essence



Systems Biology needs new, creative ways of looking at biological networks

Picasso

Westerhoff et al., London 20101110

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Westerhoff et al., London 20101110

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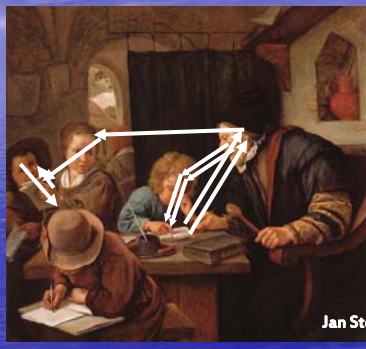
We (can) know all the components. What is missing?



Westerhoff et al., London 20101110

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Life arises not just in the isolated molecules but in their **dynamic** communication

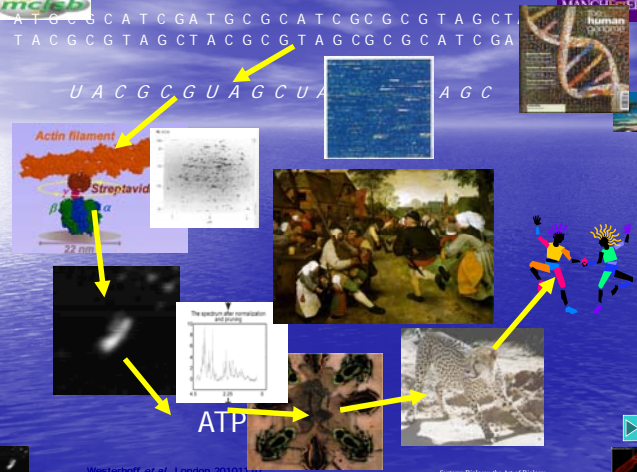


Jan Steen

Westerhoff et al., London 20101110

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ATGCCATCGATGCGCATCGCGGTAGCT
TACGCGTAGCTACGCGTAGCGGCATCGA
UACGCGUAGCUAAGC



Actin filament

Streptavidin

ATP

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Systems Biology

the Science of emergence of function in interactions

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The Arts (?)

Nontrivial ways of representing & creating thereby understanding non-material reality

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Systems Biology

the Science of emergence of function in interactions
 Understanding nonmaterial basis of functional reality
 =the Art of Biology

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Westerhoff et al., London 20101110 Systems Biology: the Art of Biology

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An example: The principle of Molecular Biology

DNA determines mRNA
 mRNA determines protein
 protein determines function

```

  graph TD
    DNA --> RNA
    RNA --> Enzyme
    Enzyme --> Process
  
```


Chemical

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Is everything prespecified by the genome?

- All cells have the same DNA
- What causes the differentiation, sharp transitions, alternation?



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Turing model

- Intracellular morphogen stimulates its own production
- Extracellular morphogen stimulates the breakdown of intracellular morphogen
- Extracellular morphogen produced also by neighboring cells

$$\frac{dX_i}{dt} = 0.01 + \frac{X_i}{1 + \frac{X_i}{5000}}$$

$$\frac{dX_i}{dt} = -X_i \cdot (0.01 + k \cdot X_{out-i})$$

$$X_{out-i} \approx k \cdot (X_{i-1} + 2X_i + X_{i+1})$$

Is it all self-organization? No; the cells use different promoters even for the repeated identical parts!

More on this:

- John Sulston (who recommended this topic)
- Jim Haseloff (self organization)
- Boris Adryan (next talk)

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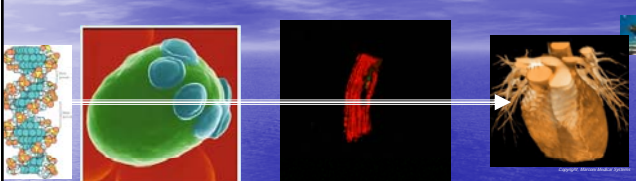
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Genomics: a bag of genes
Non functional complexity?
Can of worms?

See earlier presentations by Madan Babu and Chris Hunter

Or somehow, simplicity?

The molecular sociology of Life, exactly

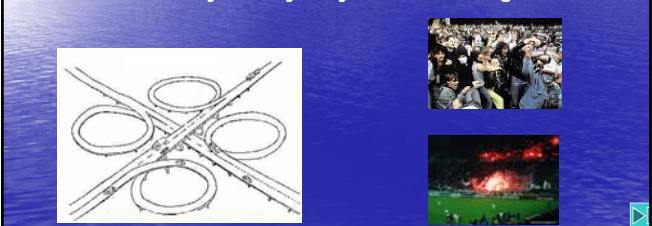


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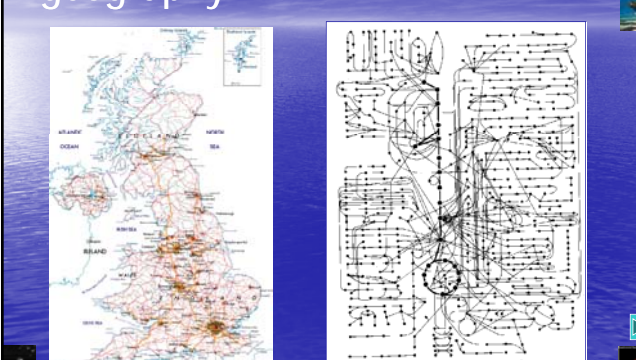
Since living organisms are networks

We need to understand them as networks, because not just any way of networking works



Westerhoff et al., London 20101110

First: a roadmap; cellular geography



The yeast consensus metabolic map: a genome scale metabolic model

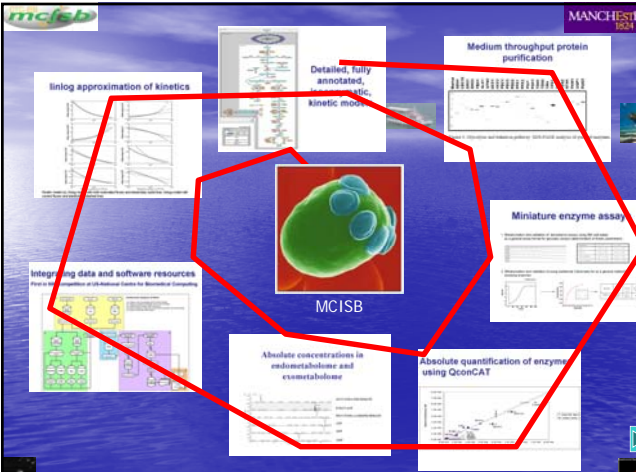
A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology

Markus J Herrgard^{1,19,20}, Neil Swainston^{2,3,20}, Paul Dobson^{3,4}, Warwick B Dunn^{3,4}, K Yalcin Arga⁵, Mikko Arvas⁶, Nils Bluthgen^{7,8}, Simon Borger⁹, Roeland Costenoble⁹, Matthias Henemann⁹, Michael Hucka¹⁰, Nicolas Le Novère¹¹, Peter Li^{2,3}, Wolfram Liebermeister⁹, Monica L Mo¹, Ana Paula Oliveira^{12,19}, Dina Petranovic^{12,19}, Stephen Pettifer^{2,3}, Evangelos Simeonidis^{3,7}, Kieran Smallbone^{3,13}, Irena Spasic^{2,3}, Dieter Weichart^{3,4}, Roger Brent¹⁴, David S Broomhead¹³, Hans V Westerhoff^{3,7,15}, Betül Kirdar⁶, Merja Penttilä⁶, Edda Klipp⁸, Bernhard O Palsson¹, Uwe Sauer⁹, Stephen G Oliver^{3,16}, Pedro Mendes^{2,3,17}, Jens Nielsen^{12,18} & Douglas B Kell^{3,4}

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linlog approximation of kinetics

Detailed, fully annotated, kinetic model

Medium throughput protein purification

Miniature enzyme assays

Integrating data and software resources

Absolute concentrations in endometabolites and exometabolites

Absolute quantification of enzymes using QconCAT


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Genomics: a bag of genes

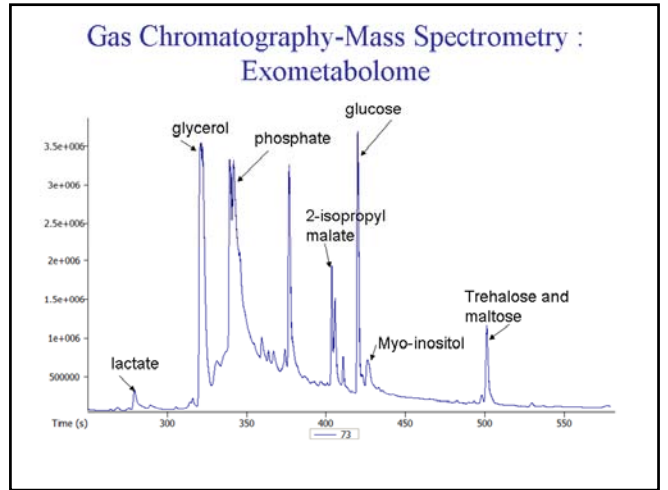
Non functional complexity?

Can of worms?



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But most of the traffic is not everywhere



Non functional complexity?

Westerhoff *et al.*, London 20101110

Neither maximally efficient
Nor simplest

Mainly alcohol
Some taste molecules

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Hypothesis

Networking enhances robustness

Michelangelo

Dynamic robustness of isolated processes = 1

Is the dynamic robustness in networks larger?

Mathematical copies of pathways in living cells on the www

Model Database

Home Model Database Site information Forums Online servers

Select model category:

The silicon cell Core models Demo models **new** JWS Online Forums

The Silicon Cell: detailed metabolic models

Pyruvate branches in <i>Lactococcus Lactis</i> - model	Hoefnagel et al. - 2002	more
Glycolysis in <i>Saccharomyces cerevisiae</i> - model	Teusink et al. - 2000	more
Glycolysis in <i>Trypanosoma brucei</i> - model	Bakker et al. - 2001	more
Sucrose accumulation in sugarcane - model	Robwer et al. - 2001	more
Bacterial phosphotransferase system - model	Robwer et al. - 2001	more
Threonine synthesis pathway in <i>E. coli</i> - model	Chastagnole et al. - 2001	more
Detailed glycolytic model in <i>Lactococcus lactis</i> - model	Hoefnagel et al. - 2002	more
Kinetics of Histone Gene Expression - model	Koster et al. - 1988	more
Glycolysis in <i>Saccharomyces cerevisiae</i> , 6 variables - model	Galazzo et al. - 1990	more
Full scale model of glycolysis in <i>Saccharomyces cerevisiae</i> - model	Hynes et al. - 2001	more
A Computational Model for Glycogenolysis in Skeletal Muscle - model	Lambeth et al. - 2002	more
Quantification of Short Term Signaling by the Epidermal GFR - model new!	Kholodenko et al. - 1999	more

Robustness of vital flux of Trypanosomes *in silico* vis-à-vis perturbation of various glycolytic steps

step	Robustness
Glctr	1.1
GAPdh	42
HK	42
PGI	1546
PFK	234
ALD	38
TPI	482
GDH	66
GPO	-251
PGK	61
PK	691
ATPase	2744
GlyK	389

Question: Is robustness higher (than 1) in networks of living cells?

Answer: Yes, most robustnesses in networks in living organisms are large; average is 468 here

Over the entire JWS live model collection

• Networks of Life enhance robustness

And, by the way We discovered a drug target...

Trypanosomiasis

NC1=NC2=C(N1)N=CN=C2Nc3ccc(cc3)N4SCC(O)S4

mcgfb NISB

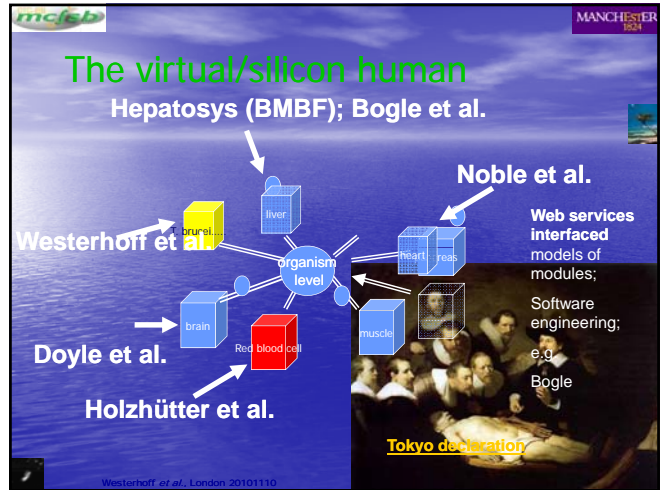
Network-based drug design:

Find the most fragile step in the network

Robustness of vital flux of Trypanosomes *vis-à-vis* perturbation of various glycolytic steps

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FEBSX-SysBio 2011

We cordially invite you to the

Joint FEBS/Systems X **Advanced Lecture Course** on

Systems Biology – From Molecules to Function

26 February 2011 – 3 March 2011: Innsbruck, Austria, EU

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Maciej Swat
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and the MCISB:

BBSRC
EPSRC