Silicon Human: oxidative stress model for aging, Parkinson's disease and precision therapies

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Infrastructure Systems Biology Europe (ISBE)



Your idea

Your intellectual property (patent, knowledge, discovery etc.)

Service from Research Infrastructure

Professional

Personalised

Cutting-edge technology

Fast

Infrastructure Systems Biology Europe (ISBE)











5)

- The Make Me My Model (M4) pillar consists of a software infrastructure that helps customers to make their various types of data (genome sequence, transcriptome, proteome, metabolome, physiological, kinetic, etc.) predictive and understood via modeling (www.isbe.nl).
- 2) The Do Me an Experiment pillar is a distributed hardware-plus-service infrastructure that performs systemsbiology quality assays as a service (M5; Make Me My Mass Spectra Measurements, enzyme kinetics, metabolomics, and epigenetics will be soon available. For the time being, there is a Systems Metabolomics service at ISBE.IT (www.sysbio.it/isbe): a complete metabolomic platform to perform ad hoc experiments, coupled with constraint-based modeling approach.
- 3) The Live Model Repository (LMR) of ISBE is a software infrastructure of interconnectable, systems-biologyquality kinetic models through JWS Online (https://jjj.bio.vu.nl/) and COSYS (sysbio.it/cosys/), where users can perform construction, modification, and simulation of kinetic models, and storage of curated ones (JWS), or define mathematical models of biological systems and perform constraint-based (e.g., Flux Balance Analysis) and mechanism-based dynamic simulations (either deterministic or stochastic), drastically accelerated by GPUs (COSYS).
- 4) The Data and Model Stewardship of ISBE called FAIRDOM (http://fair-dom.org). The FAIRDOM Project was started under the auspices of the ERA-NET programme ERASysAPP and ISBE, jointly funded by CH, DE, NL and UK. FAIRDOM assists researchers to be in control of collecting, managing, storing, and publishing data, models, and operating procedures. FAIRDOM takes responsibility for the Stewardship of research assets services of ISBE.
 - Help Me to Model (HMTM) provides training to customers wishing to make models themselves, in online or workshop tutorials (www.isb.nl).

Findable, Accessible, Interoperable, Reusable (FAIR) Model management for ISBE services in FAIRDOM



ISBE.NL at EOSC-Life (European Open Science Cloud)



CORBEL supported services: Integration of Systems Biological Infrastructures



Contents

- Virtual Human the fate of Systems Biology
- How reconstruction of biological behavior in silico leads to delegation of our understanding to computer models
- Top-down, middle-out and bottom-up aproaches
- What does help us to build Virtual Human
- What does Virtual Human bring to us
- Philosophical aspects of Virtual Human
-with biological examples

Reactive Oxygen Species and Aging COVID-19 pandemics modelling



Reductionism (one gene -> one disease)

Inferred from the central dogma of molecular biology DNA (cause)=>RNA=>Protein (effect)



Circular causality in biology

The cell manages both storage and reading DNA information as a whole; metabolites and proteins regulate transcription



An example of circular causality

BIOLOGY OF REPRODUCTION **72**, 510–515 (2005) Published online before print 6 October 2004. DOI 10.1095/biolreprod.104.031302

Cytoplasmic Impact on Cross-Genus Cloned Fish Derived from Transgenic Common Carp (*Cyprinus carpio*) Nuclei and Goldfish (*Carassius auratus*) Enucleated Eggs¹

Yong-Hua Sun, Shang-Ping Chen, Ya-Ping Wang, Wei Hu, and Zuo-Yan Zhu²

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Emergentism in biology

By Broad, C.D. (1925). The Mind and Its Place in Nature, London: Routledge & Kegan Paul, first edition



Problem, unsolved by C.D. Broad



Carbon atoms in the diamond

VS

Weak emergence

Arenerative Arener

"erkenne dich selbst"

Gnothi Seauton (Υνωθι σεαυτον)

Strong emergence

Broad, C.D. (1925). *The Mind and Its Place in Nature*, London: Routledge & Kegan Paul, first edition



The more information about state dependency is required to reconstruct the emergence - the stronger is the emergence



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High state-dependency of component properties e.g. interactions between proteins A and B depends on

- Other components (C,D,E,F...)
- Hysteresis
- Flow of mass and energy through the system
- Initial and boundary conditions, etc.

The information about state dependency might be described in the form of mathematical equations

A70

	$ \begin{pmatrix} \frac{d(A_{555})}{dt} = kf_{555} \cdot [A_{546}] \cdot [A_{549}] \\ \frac{d(A_{555})}{dt} = kf_{555} \cdot [A_{546}] \cdot [A_{549}] \\ \frac{d(A_{1000})}{dt} = kf_{1000} \cdot [A_{999}] \cdot [A_{998}] \\ \frac{d(A_{1002})}{dt} = kf_{1001} \cdot [A_{1000}] \cdot [A_{1001}] $				
60	solve				



A₉₉₈

Systems Biology – holism and reductionism at the same time

 A_{999}

"All science is either physics or stamp collecting."

Ernest Rutherford, physicist, born August 30, 1871



Dobson's Improbable Quote of the Day



How emergent properties of system relate to each other:





How properties of system emerge:

 $E_k=3/2k*T$





Biology: from "Stamp collecting" to "physics"





List of genes associated with 6000 genetic diseases:

Phenylalanine hydroxylase (PAH)

Disease Phenylketonuria (PKU) **Cystic fibrosis**

Sickle-cell anemia

Albinism, oculocutaneous, type II

Huntington's disease

Myotonic dystrophy type 1

Hypercholesterolemia, autosomal dominant, Autosor Orginal research type B

Type of Inheritance Autosomal recessive Autosomal recessive

Autosomal recessive

Autosor Autoso Autosor



Gene Responsible

Molecular Bi

journal homepage: www.elsevier.com/locate/pbiomolbio

Computing life: Add logos to biology and bios to physics

Autoco, Alexey Kolodkin^{a,b,*}, Evangelos Simeonidis^{a,b}, Hans V. Westerhoff^{c,d,e}

Systems Biology: Virtual Human instead of a single equation









William of Occam (1285-1349): "One should not postulate (pose) more things without necessity" (*Pluralitas non est ponenda sine necessitate*)

Which model is more likely to be correct?



D

B









Systems Biology

Hans V. Westerhoff (at the beginning of the XXI century): One should not remove things without necessity (*Pluralitas non est eliminanda sine necessitate*)

More likely to be correct



Alexey Kolodkin^{a,b,*}, Evangelos Simeonidis^{a,b}, Hans V. Westerhoff^{c,d,e}



Virtual Human is a model (a projection of one system to another system)



But all our "Data" are also "Models"; it is what is "taken" rather than what is "given"



Digital/Virtual/Silicon Human



Universal building blocks for all biological systems



CH ₂ OH	
Н	-0 <u>H</u>
ОН	НОН
⊺ H	OH
aluco	se

Abb	eviation	Name	Side-chain	рка
Α	ala	Alanine	hydrophobic	
С	cys	Cysteine	hydrophobic	8.5
D	asp	Aspartic acid	negative	4.4
E	glu	Glutamic acid	negative	4.4
F	phe	Phenylalanine	hydrophobic	
G	gly	Glycine	hydrophobic	
H	his	Histidine	positive	6.5
Ι	ile	Isoleucine	hydrophobic	
K	lys	Lysine	positive	10.0
L	leu	Leucine	hydrophobic	
M	met	Methionine	hydrophobic	
N	asn	Asparagine	polar	
Р	pro	Proline	hydrophobic	
Q	gln	Glutamine	polar	
R	arg	Arginine	positive	12.0
S	ser	Serine	polar	
Т	thr	Threonine	polar	
W	trp	Tryptophan	hydrophobic	
Y	tyr	Tyrosine	polar	10.0
V	val	Valine	hydrophobic	

xv



"Blue-print" modelling



AK1



Cell differentiation

Organisms differentiation







AK1 Alexey KOLODKIN, 7/15/2014

Hourglass principle in blue-print modelling

Diverse information for building the model (al lot of Data)



Model instantiations specific for: species, diseases, persons

We model "ideal" behavior of homeostatic systems

Robustness through networking



Shukhov tower, 350m (reduced to 160 m), Moscow, 1920-1922

Disease as a network perturbation



Current Opinion in Biotechnology Volume 21, Issue 4, August 2010, Pages 566-571



Diseases as network perturbations

Antonio del Sol ¹, Rudi Balling ¹ 🖾, Lee Hood ², David Galas ²

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https://doi.org/10.1016/j.copbio.2010.07.010

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Reconstruction of emergent behavior and state-dependency of components properties. Example.

npj Systems Biology and Applications

www.nature.com/npjsba

ARTICLE OPEN ROS networks: designs, aging, Parkinson's disease and precision therapies

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Complexity and state-dependency in Parkinson's disease



Insight and Reproducibility are compromised if we take fragments



A system should be taken as a whole

Computer and AI will do it better than human brain





Robot-scientist is working in Manchester





We start with ROS (Reactive Oxygen Species)





Step by step, we add new network features and observe new emergent properties (design principles study)





Step by step, we add new network features and observe new emergent properties (design principles study)





Initial module: Mitochondrial damage and ROS form positive feedback





Design 1: Adding mitophagy and ROS removal







Design 1: With mitophagy and ROS removal





Design 1: summary

S	teady state emerg	led No s	No structural robustness No dynamic robustness		
		no design	design 1		
	Feature	-	Mitophagy and ROS removal		
es d	Steady state	-	+		
opertio nerge	Structural robustness	-	-		
Pre	Dynamic robustness	-	-		

uni.lu

LCSB

Design 2: Healthy mitochondria is variable



Design 2: Healthy mitochondria is variable





Design 2: Healthy mitochondria is variable





Design 2: summary



Design 3: Adding Nrf2-keap1 and p62 feedback



Design 3: Nrf2-keap1 and p62 feedback





Design 3: summary

Homeostasis emerged

		no design	design 1	design 2	design 3
	Feature	-	Mitophagy and ROS removal	Healthy mitochondri a is variable	Nrf2-Keap1 and p62 feedback
rged	Steady state	-	+	+	+
erties eme	Structural robustness	-	-	+	+
Prop	Homeostasis	-	-	-	+

We continue design principle studdies

Robustness with respect to the second pulse of ROS

		no design	design 1	design 2	design 3	design 4	design 5
	Feature	-	Mitophagy and ROS removal	Healthy mitochondri a is variable	Nrf2-Keap1 and p62 feedback	NFkB signaling for mitochondri al repair	DJ1 balancing responses
	Steady state	-	+	+	+	+	+
.ged	Structural robustness	-	-	+	+	+	+
me	Homeostasis	-	-	-	+	+	+
rties e	Dynamical robustness	-	-	+	-	+	+
Prope	Robustness with respect to the second pulse of ROS	70 p 108	Dages of Supplementary Material, plots, 138 COPASI models				

uni.

Detailed ROS model





Validation of ROS model in terms of response to menadione and hydrogen peroxide



Design principles were checked again

Emergent behavior reconstructed in silico

Preconditioning to oxidative stress (memory)





Sensitivity analysis of the dependence of steady state ROS levels on various parameters



Life-time control coefficient

Process	Control on time when ATP=0.5
Synthesis of mitochondria	-2.6
KEAP1 synthesis	-1.8
p62RNA-ase	-1.7
p62 synthesis	1.7
p62 transcription	1.7
KEAP1 damage	1.5
Degradation of damaged mitochondria	1.5
Synthesis of apoptotic machinery	1.5
Synthesis of antioxidant proteins	1.5
Transcription of antioxidant genes	1.5
ROS removal	1.5
Degradation of apoptotic machinery	-1.5
Degradation of antioxidant mRNA	-1.5
ROS synthesis	-1.5
Degradation of antioxidant protein	-1.5
Nuclear export of NRF2	-1.4
Repair of KEAP1	-1.4
NRF2 synthesis	1.4
NRF2 nuclear import	1.4
Degradation of damaged KEAP1	1.4
Binding of KEAP1 to NRF2	-1.2
Oxidative phosphorylation	-1.1
Damaging of mitochondria by ROS	1.1
Cellular ATP consumption	1.1
Generation of damaging factors	-1.0



Sum of all individual time-control coefficients = Time-control by simultaneous activation of all molecular processes = -1

Best network-based target processes for drugs to retard aging



a-synuclein







Aging, Parkinson's disease and personalised medicine DJ1 DJ1 healthy DJ1 down ATP mM DJ1 out Comp DJ1 out Time, years



p62











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