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Systems Biology in Biotech & Pharma

A Changing Paradigm

Springer

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Dedicated to my "teachers" and friends, the late Zdeněk Fencl (Prague), Arthur E. Humphrey, Elmer L. Gaden and Godfred E. Tong (USA) who influenced and shaped my professional career (AP)

Contents

Abbreviations

3D	Three-dimensional
3D/4D QSAR	Three dimensional/four dimensional QSAR
3D-QSAR	Three dimensional QSAR
ABC	Bayesian computation
ABM	Agent-based methods
ADMET	Absorption, distribution, metabolism, excretion, and toxicity
AMS	Accelerator mass spectrometry
ANN	Artificial Neural Networks
anti-CD40L	Antibody raised against CD40L region
ARACNE	Algorithm for the reconstruction of accurate cellular networks
BI	Bioinformatics
BLA	Biologic application
BOSS	Biological objective solution search
BSR	Biochemical system (network) reconstruction
CCA	Canonical correlation analysis
CD14-/-	Type of mice
CDD	Controlled drug delivery
CellML	Mark-up language
CG	Coarse-graining or CG computing
CNI	Correlation network inference
COAST	Complex automata for modeling and simulation of complex systems
COMBINE	Comparative binding energy
CSB	Computational systems biology
CSDD	Center for the study of drug development (Tufts)
DD	Drug discovery
DDD	Drug discovery and development

DDS	Drug delivery systems
DDv	Drug development
DOS	Diversity-oriented synthesis
dsRNA	Double strand RNA
EBI	European bioinformatics institute
ED	Enrichment designs
EGFR	Endothelial growth factor receptor
EPR	Passive uptake
ERK	Extracellular regulated kinase
FBA	Flux balance analysis
FBDD	Fragment based DD
FCR	Fluorochromatic reaction fluorescence
FDA	Food and drug association
FRET	Fluorescence resonance energy transfer
GNR	Gene regulatory network
GO	Gene ontology
hPXR	Humanized transgenic mice
HQSAR	Hologram quantitative structure-activity relationships
HT	High throughput
HTS	High throughput screening
iFBA	Integrated dynamic FBA
IFN-β	Interferon beta
IL-12	Interleukin 12
IL-15	Interleukin 15
JWS	Journal of web semantics
KEGG	Kyoto encyclopedia of genes and genomes
KNN	K-nearest neighbors
LDA	Linear discriminant analysis
MARS	Splines
MBDD	Model based drug design
MCA	Metabolic control analysis
MD	Molecular dynamics
MINDy	Modulator inference by network dynamics
miRNA	MicroRNA
MM	Molecular mechanics
MMR	DNA mismatch repair
MoA	Mode of action
MS	Multiple sclerosis
MVDA	Multivariate data analysis
NB	Naïve Bayes
NDA	New drug application
NME	New medical entity
NMR	Nuclear magnetic resonance

NOD	Nude mouse
OBRC	Online bioinformatics resources collection
ODE	Ordinary differential equation
OiCR	Ontario institute for cancer research
OMICS	Discipline of science and engineering for analyzing the interactions of biological information objects
PAT	Process analytical technology
PCA	Principal components analysis
PD	Parkinson disease
PD	Pharmacodynamics
PEGylation	Attachment of polyethylene glycol (PEG)
PEM	Protein epitope mimetic
PET	Positron emission tomography
PGN	Pharmacogenomics
PhRMA	Pharmaceutical research and manufacturers of America
PI3K	Phosphoinositide-3-kinase
PK	Pharmacokinetics
PKPD	Combined PK and PD
PLS	Partial least-squares
PM	Pharmacometrics
PromoLign	Simulation tool
PTEN	Phosphatase and tensin homolog
PupaSNP	Simulation tool
QbD	Quality by design
QSAR	Quantitative structure-activity relationship
R&D	Research and development
R03	Rule of three
RA	Entelos rheumatoid arthritis
RAW	Mouse leukaemic monocyte macrophage cell line
RDD	Re-randomization design
ReguLign	Simulation tool
R-L	Receptor-ligand
RNAi	RNA interference
RNI	Reaction network inference
RNIDD	Reaction network inference for drug discovery
Ro5	Rule of five
ROT	Rule-of-thumb
RPART	Recursive partitioning and regression trees
SAR	QSAR
SB	Systems biology
SBML	Systems biology markup language
siRNA	Small nterfering RNA
SG	Systems genetics

SNP	Single nucleotide polymorphism
SSM	Scale separation map
SVM	Support vector machines
TGF-β	Transformation growth factor beta
TNF-α	Tumor necrosis factor alfa
uHTS	Ultra high throughput screening
WW2	Second world war

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Abstract

Systems Biology (SB) is suite of technologies and methodologies that resulted, conceptually, from the merging of two basic paradigms, reductionism and holism. It represents a combination of reductionist and holistic approaches to the relationships among the elements of a system, with the goal of identifying its emergent properties and defining, quantitatively, molecular, cellular, tissue, organ and whole body processes. One manifestation of SB is as a tool for hypothesis generation about a system that is typically too large and complex to understand by simple reasoning.

The US is currently well ahead of the rest of the world in the development and application of SB and its principles especially as they pertain to basic medical research and development. This lead is largely due to an earlier start in the academic arena (7–9 years ago in US vs. 4–5 years elsewhere; Rubenstein 2008). However, there is evidence of rapid development in both the UK/EU and Japan and the gap is narrowing, particularly in UK. From an industrial point of view, the Pharmaceutical Industry based in the US and UK can capitalize on these opportunities and gain the benefits of this technology. Early and sustained investments in SB and its enabling technologies will likely produce financial rewards for any pharma company so inclined. Many big Pharma companies have already invested in SB and Bioinformatics (BI) (for definitions of SB and BI see Chap. 1) and are set to maintain their lead. The industrial significance of SB is thus clear.

This review intends to educate a large population of cell and molecular biologists in the use of the quantitative tools that are available to them to solve the critical problems they face. Many educational institutions (and particularly their medical divisions) at present are heavily business-oriented realize that in this particular industrial environment that dollar counts. It is thus important that biologists recognize early in their research the utility of SB and how this approach can help to generate new therapeutic leads and substances useful for human health. Educational curricula in the life sciences have typically been based on the atomistic belief that one can decompose complex systems into their components and that a detailed investigation of each these components individually will in itself lead to novel biological insights. Indeed this is true in numerous instances. However, increasing acknowledgment of the importance of studying whole systems, as well as their components, has led to an emphasis on teaching not just a reductionist view of biology, but also a complementary constructionist view. {Note: Bioprocess engineering issues, as related to a systems approach at manufacturing, are not included in this review. However, included in our broader definition, we do incorporate some of the issues surrounding BI in this review}. Overall, we attempt to answer a question: Can Systems Biology deliver on academic funding and business profits?