

**Spring 2021– Epigenetics and Systems Biology**  
**Lecture Outline – Systems Biology**  
**Michael K. Skinner – Biol 476/576**  
**10:35-11:50 am, Tuesdays (1/19/21) Introduction Zoom Session**  
**January, 2021**  
**Weeks 1 and 2**

### **Systems Biology**

- History and Definitions
- Reductionism/ Genetic Determination
- Holism/ Emergentism/ Homeostasis or Robustness
- Revolutionary and Evolutionary Systems Biology
- Networks and Computational Biology
- Basic Molecular and Cellular Components

### **Required Reading**

Knepper et al. (2014) Systems biology versus reductionism in cell physiology. *Am J Physiol Cell Physiol* 307:C308-C309.

Wolfe CT. Chance between holism and reductionism: tensions in the conceptualisation of Life. *Prog Biophys Mol Biol.* 2012 Sep;110(1):113-20.

Zupanic A, Bernstein HC, Heiland I. Systems biology: current status and challenges. *Cell Mol Life Sci.* 2020 Feb;77(3):379-380.

### **Background Book References**

**James A. Marcum (2009) The Conceptual Foundations of Systems Biology, Nova Science Publishers, Inc.**

Eberhard Voit (2012) *A First Course in Systems Biology*, Garland Science

Capra and Luisi (2014) *The Systems View of Life*, Cambridge University Press.

Leonie Ringrose (2017) *Epigenetics and Systems Biology*, Academic Press

### **Literature**

Gauthier J, Vincent AT, Charette SJ, Derome N. A brief history of bioinformatics. *Brief Bioinform.* 2019 Nov 27;20(6):1981-1996.

Tusscher KT. Of mice and plants: Comparative developmental systems biology. *Dev Biol.* 2020 Apr 1;460(1):32-39.

- Wagner DE, Klein AM. Lineage tracing meets single-cell omics: opportunities and challenges. *Nat Rev Genet.* 2020 Jul;21(7):410-427.
- Shukla N, Merigó JM, Lammers T, Miranda L. Half a century of computer methods and programs in biomedicine: A bibliometric analysis from 1970 to 2017. *Comput Methods Programs Biomed.* 2020 Jan;183:105075.
- Vogt H, Hofmann B, Getz L. The new holism: P4 systems medicine and the medicalization of health and life itself. *Med Health Care Philos.* 2016 Jun;19(2):307-23.
- Fulvio Mazzocchi F. Complexity and the reductionism-holism debate in systems biology. *Wiley Interdiscip Rev Syst Biol Med.* Sep-Oct 2012;4(5):413-27.
- Scheid V, Holism, Chinese Medicine and Systems Ideologies: Rewriting the Past to Imagine the Future. Editors: Whitehead, Woods, Atkinson, Macnaughton, Richards, In: *The Edinburgh Companion to the Critical Medical Humanities.* Edinburgh: Edinburgh University Press; 2016 Jun 30. Chapter 3. Wellcome Trust-Funded Monographs and Book Chapters.
- Sato N. "Life-bearing molecules" versus "life-embodying systems": Two contrasting views on the what-is-life (WIL) problem persisting from the early days of molecular biology to the post-genomic cell- and organism-level biology. *Biosystems.* 2018 May;167:24-32.
- Gatherer D. So what do we really mean when we say that systems biology is holistic? *BMC Syst Biol.* 2010 Mar 12;4:22.
- Krecek J. Holism and life manifestations: molecular and space-time biology. *Physiol Res.* 2010;59(2):157-63.
- Deichmann U. Hierarchy, determinism, and specificity in theories of development and evolution. *Hist Philos Life Sci.* 2017 Oct 16;39(4):33.
- Kienle G, Helmut Kiene H. From Reductionism to Holism: Systems-oriented Approaches in Cancer Research. *Glob Adv Health Med.* 2012 Nov;1(5):68-77.
- Delker RK, Richard S Mann RS. From Reductionism to Holism: Toward a More Complete View of Development Through Genome Engineering. *Adv Exp Med Biol.* 2017;1016:45-74.
- Federoff HJ, Gostin LO. Evolving from reductionism to holism: is there a future for systems medicine? *JAMA.* 2009 Sep 2;302(9):994-6.
- Aggestam F. Framing the ecosystem concept through a longitudinal study of developments in science and policy. *Conserv Biol.* 2015 Aug;29(4):1052-64.
- Kuchling F, Friston K, Georgiev G, Levin M. Morphogenesis as Bayesian inference: A variational approach to pattern formation and control in complex biological systems. *Phys Life Rev.* 2020 Jul;33:88-108.
- Tenenbaum D, Marrone JI, Grecco HE, AC. Robustness in spatially driven bistability in signaling systems. *Sci Rep.* 2020 Mar 27;10(1):5591.
- Gorochoowski TE, Hauert S, Kreft J-U, et al. Toward Engineering Biosystems With Emergent Collective Functions. *Front Bioeng Biotechnol.* 2020 Jun 26;8:705.
- Benson DL. Of Molecules and Mechanisms. *J Neurosci.* 2020 Jan 2;40(1):81-88.
- Dias R, Torkamani A. Artificial intelligence in clinical and genomic diagnostics. *Genome Med.* 2019 Nov 19;11(1):70.
- Mercatelli D, Scalambra L, Triboli L, et al. Gene regulatory network inference resources: A practical overview. *Biochim Biophys Acta Gene Regul Mech.* 2020 Jun;1863(6):194430.
- Kuenzi BM, Ideker T. A census of pathway maps in cancer systems biology. *Nat Rev Cancer.* 2020 Apr;20(4):233-246.
- Silverman EK, Schmidt HHHW, Anastasiadou E, et al. Molecular networks in Network Medicine: Development and applications. *Wiley Interdiscip Rev Syst Biol Med.* 2020 Nov;12(6):e1489.

- Blencowe M , Karunanayake T, Wier J, Hsu N, Yang X. Network Modeling Approaches and Applications to Unravelling Non-Alcoholic Fatty Liver Disease. *Genes (Basel)*. 2019 Nov 24;10(12):966.
- Conte F, Fiscon G, Licursi V, Bizzarri D, D'Antò T, Farina L, Paci P. A paradigm shift in medicine: A comprehensive review of network-based approaches. *Biochim Biophys Acta Gene Regul Mech*. 2020 Jun;1863(6):194416.
- Ramos PIP, Arge LWP, Lima NCB, Fukutani KF, de Queiroz ATL. Leveraging User-Friendly Network Approaches to Extract Knowledge From High-Throughput Omics Datasets. *Front Genet*. 2019 Nov 13;10:1120.
- Lun X-K, Bodenmiller B. Profiling Cell Signaling Networks at Single-cell Resolution. *Mol Cell Proteomics*. 2020 May;19(5):744-756.
- Gedeon T. Multi-parameter exploration of dynamics of regulatory networks. *Biosystems*. 2020 Apr;190:104113.
- Verkhivker GM, Agajanian S, Hu G , Tao P. Allosteric Regulation at the Crossroads of New Technologies: Multiscale Modeling, Networks, and Machine Learning. *Front Mol Biosci*. 2020 Jul 9;7:136.
- Rukhlenko O, Kholodenko BN, Kolch W. Systems biology approaches to macromolecules: the role of dynamic protein assemblies in information processing. *Curr Opin Struct Biol*. 2020 Oct 23;67:61-68.
- Ma C-Y, Liao C-S. A review of protein-protein interaction network alignment: From pathway comparison to global alignment. *Comput Struct Biotechnol J*. 2020 Sep 18;18:2647-2656.
- Foray C , Barca C , Backhaus P, et al. Multimodal Molecular Imaging of the Tumour Microenvironment. *Adv Exp Med Biol*. 2020;1225:71-87.
- Eicher T, Kinnebrew G, Patt A, et al. Metabolomics and Multi-Omics Integration: A Survey of Computational Methods and Resources. *Metabolites*. 2020 May 15;10(5):202.
- Infante T, Francone M, De Rimini ML, et al. Machine learning and network medicine: a novel approach for precision medicine and personalized therapy in cardiomyopathies. *J Cardiovasc Med (Hagerstown)*. 2020 Sep 3.
- Wood SH. How can a binary switch within the pars tuberalis control seasonal timing of reproduction? *J Endocrinol*. 2018 Oct 1;239(1):R13–R25.
- Sieriebriennikov B, Sommer RJ. Developmental Plasticity and Robustness of a Nematode Mouth-Form Polyphenism. *Front Genet*. 2018 Sep 11;9:382.
- Sarma GP, Lee CW, Portegys T, Ghayoomie V, et al. OpenWorm: overview and recent advances in integrative biological simulation of *Caenorhabditis elegans*. *Philos Trans R Soc Lond B Biol Sci*. 2018 Sep 10;373(1758).
- Kiani NA, Shang MM, Zenil H, Tegner J. Predictive Systems Toxicology. *Methods Mol Biol*. 2018;1800:535-557.
- Wohlgemuth R. Horizons of Systems Biocatalysis and Renaissance of Metabolite Synthesis. *Biotechnol J*. 2018 Jun;13(6):e1700620.
- McLeod C, Nerlich B. Synthetic biology, metaphors and responsibility. *Life Sci Soc Policy*. 2017 Aug 29;13(1):13..
- Delker RK, Mann RS. From Reductionism to Holism: Toward a More Complete View of Development Through Genome Engineering. *Adv Exp Med Biol*. 2017;1016:45-74.
- Avramouli A, Vlamos PM. Integrating Omic Technologies in Alzheimer's Disease. *Adv Exp Med Biol*. 2017;987:177-184.
- Pezzulo G, Levin M. Top-down models in biology: explanation and control of complex living systems above the molecular level. *J R Soc Interface*. 2016 Nov;13(124).

- Aury-Landas J, Marcelli C, Leclercq S, Boumédiène K, Baugé C. Genetic Determinism of Primary Early-Onset Osteoarthritis. *Trends Mol Med*. 2016 Jan;22(1):38-52.
- Holbrook JD. An epigenetic escape route. *Trends Genet*. 2015 Jan;31(1):2-4.
- Sato N. "Life-bearing molecules" versus "life-embodying systems": Two contrasting views on the what-is-life (WIL) problem persisting from the early days of molecular biology to the post-genomic cell- and organism-level biology. *Biosystems*. 2018 May;167:24-32.
- Chen J, Coppola G. Bioinformatics and genomic databases. *Handb Clin Neurol*. 2018;147:75-92.
- Liang X, Feswick A, Simmons D, Martyniuk CJ. Environmental toxicology and omics: A question of sex. *J Proteomics*. 2018 Feb 10;172:152-164.
- Dimitrakopoulos L, Prassas I, Diamandis, Charames GS. Onco-proteogenomics: Multi-omics level data integration for accurate phenotype prediction. *Crit Rev Clin Lab Sci*. 2017 Sep;54(6):414-432.
- Wilson BJ, Miller FA, Rousseau F. Controversy and debate on clinical genomics sequencing-paper 1: genomics is not exceptional: rigorous evaluations are necessary for clinical applications of genomic sequencing. *J Clin Epidemiol*. 2017 Dec;92:4-6.
- Mulder NJ, Adebisi E, Adebisi M, et al. Development of Bioinformatics Infrastructure for Genomics Research. *Glob Heart*. 2017 Jun;12(2):91-98.
- Korcsmaros T, Schneider MV, Superti-Furga G. Next generation of network medicine: interdisciplinary signaling approaches. *Integr Biol (Camb)*. 2017 Feb 20;9(2):97-108.
- Aebersold R, Mann M. Mass-spectrometric exploration of proteome structure and function. *Nature*. 2016 Sep 15;537(7620):347-55.
- Vendrell X, Escribà MJ. The model of "genetic compartments": a new insight into reproductive genetics. *J Assist Reprod Genet*. 2018 Nov 12. doi: 10.1007/s10815-018-1366-3. [Epub ahead of print]
- Goyal A, Myacheva K, Groß M, Klingenberg M, Duran Arqué B, Diederichs S. Challenges of CRISPR/Cas9 applications for long non-coding RNA genes. *Nucleic Acids Res*. 2017 Feb 17;45(3):e12.
- Payne JL, Wagner A. The causes of evolvability and their evolution. *Nat Rev Genet*. 2018 Nov 1. doi: 10.1038/s41576-018-0069-z. [Epub ahead of print]
- Carthew RW, Agbu P, Giri R. MicroRNA function in *Drosophila melanogaster*. *Semin Cell Dev Biol*. 2017 May;65:29-37.
- Goldstein B. The Emergence of the Tardigrade *Hypsibius exemplaris* as a Model System. *Cold Spring Harb Protoc*. 2018 Nov 1;2018(11):pdb.emo102301.
- Sigston EAW, Williams BRG. An Emergence Framework of Carcinogenesis. *Front Oncol*. 2017 Sep 14;7:198.
- Dana H, Chalbatani GM, Mahmoodzadeh H, et al. Molecular Mechanisms and Biological Functions of siRNA. *Int J Biomed Sci*. 2017 Jun;13(2):48-57.
- Hosseini ES, Meryet-Figuere M, Sabzalipoor H, Kashani HH, Nikzad H, Asemi Z. Dysregulated expression of long noncoding RNAs in gynecologic cancers. *Mol Cancer*. 2017 Jun 21;16(1):107.
- Nobile MS, Cazzaniga P, Tangherloni A, Besozzi D. (2016) Graphics processing units in bioinformatics, computational biology and systems biology. *Brief Bioinform*. Jul 8. pii: bbw058. [Epub ahead of print]
- Turaev D, Rattei T. (2016) High definition for systems biology of microbial communities: metagenomics gets genome-centric and strain-resolved. *Curr Opin Biotechnol*. Jun;39:174-81.
- Niu F, Wang DC, Lu J, Wu W, Wang X. (2016) Potentials of single-cell biology in identification and validation of disease biomarkers. *J Cell Mol Med*. 20(9):1789-95

- Petta S, Valenti L, Bugianesi E, Targher G, Bellentani S, Bonino F; Special Interest Group on Personalised Hepatology of the Italian Association for the Study of the Liver (AISF); Special Interest Group on Personalised Hepatology of Italian Association for Study of Liver AISF. (2016) A "systems medicine" approach to the study of non-alcoholic fatty liver disease. *Dig Liver Dis.* 48(3):333-42.
- Bouchard C. (2015) Adaptation to Acute and Regular Exercise: From Reductionist Approaches to Integrative Biology. *Prog Mol Biol Transl Sci.* 135:1-15.
- de Vargas Roditi L, Claassen M. (2015) Computational and experimental single cell biology techniques for the definition of cell type heterogeneity, interplay and intracellular dynamics. *Curr Opin Biotechnol.* 34:9-15.
- Benner SA, Karalkar NB, Hoshika S, Laos R, Shaw RW, Matsuura M, Fajardo D, Moussatche P. (2016) Alternative Watson-Crick Synthetic Genetic Systems. *Cold Spring Harb Perspect Biol.* 1;8(11).
- Nemhauser JL, Torii KU. (2016) Plant synthetic biology for molecular engineering of signalling and development. *Nat Plants.* 2;2:16010.
- Shah E. (2016) A tale of two biographies: the myth and truth of Barbara McClintock. *Hist Philos Life Sci.* 38(4):18.
- Pezzulo G, Levin M. (2016) Top-down models in biology: explanation and control of complex living systems above the molecular level. *J R Soc Interface.* 13(124). pii: 20160555.
- Kesić S. (2016) Systems biology, emergence and antireductionism. *Saudi J Biol Sci.* 23(5):584-91.
- Margineanu DG. (2016) Neuropharmacology beyond reductionism - A likely prospect. *Biosystems.* 141:1-9.
- Loor JJ, Vailati-Riboni M, McCann JC, Zhou Z, Bionaz M. (2015) TRIENNIAL LACTATION SYMPOSIUM: Nutrigenomics in livestock: Systems biology meets nutrition. *J Anim Sci.* 93(12):5554-74.
- Lista S, Khachaturian ZS, Rujescu D, Garaci F, Dubois B, Hampel H. (2016) Application of Systems Theory in Longitudinal Studies on the Origin and Progression of Alzheimer's Disease. *Methods Mol Biol.* 1303:49-67.
- Hilbert A. (2016) Weight Stigma Reduction and Genetic Determinism. *PLoS One.* 15;11(9):e0162993.
- Casane D, Rétaux S. (2016) Evolutionary Genetics of the Cavefish *Astyanax mexicanus*. *Adv Genet.* 95:117-59.
- Arribas-Ayllon M. (2016) After geneticization. *Soc Sci Med.* 159:132-9.
- Buecher B. (2016) Colorectal adenomatous polyposis syndromes: Genetic determinism, clinical presentation and recommendations for care. *Bull Cancer.* 2016 Feb;103(2):199-209.
- Scheid V. (2016) Holism, Chinese Medicine and Systems Ideologies: Rewriting the Past to Imagine the Future. In: Atkinson S, Macnaughton J, Richards J, authors; Whitehead A, Woods A, editors. *The Edinburgh Companion to the Critical Medical Humanities*. Edinburgh (UK): Edinburgh University Press; 2016 Jun. Chapter 3. Wellcome Trust-Funded Monographs and Book Chapters.
- Vogt H, Hofmann B, Getz L. (2016) The new holism: P4 systems medicine and the medicalization of health and life itself. *Med Health Care Philos.* 19(2):307-23.
- Torday JS. (2015) A central theory of biology. *Med Hypotheses.* 85(1):49-57.
- Díaz-Muñoz SL, Boddy AM, Dantas G, Waters CM, Bronstein JL. (2016) Contextual organismality: Beyond pattern to process in the emergence of organisms. *Evolution.* 70(12):2669-2677.
- Alanis-Lobato G, Mier P, Andrade-Navarro MA. (2016) Efficient embedding of complex networks to hyperbolic space via their Laplacian. *Sci Rep.* 22;6:30108.

- Scarpa JR, Jiang P, Losic B, et al. (2016) Systems Genetic Analyses Highlight a TGF $\beta$ -FOXO3 Dependent Striatal Astrocyte Network Conserved across Species and Associated with Stress, Sleep, and Huntington's Disease. *PLoS Genet.* 8;12(7):e1006137.
- Adachi N, Senda T, Horikoshi M. (2016) Uncovering ancient transcription systems with a novel evolutionary indicator. *Sci Rep.* 16;6:27922.
- Versluis F, van Esch JH, Eelkema R. (2016) Synthetic Self-Assembled Materials in Biological Environments. *Adv Mater.* 28(23):4576-92.
- Igamberdiev AU, Shklovskiy-Kordi NE. (2016) Computational power and generative capacity of genetic systems. *Biosystems.* 2016 Apr-May;142-143:1-8.
- Kaufman CK, Mosimann C, Fan ZP, et al. (2016) A zebrafish melanoma model reveals emergence of neural crest identity during melanoma initiation. *Science.* 29;351(6272):aad2197.
- Olivier BG, Swat MJ, Moné MJ. (2016) Modeling and Simulation Tools: From Systems Biology to Systems Medicine. *Methods Mol Biol.* 1386:441-63.
- Amirkhah R, Farazmand A, Wolkenhauer O, Schmitz U. (2016) RNA Systems Biology for Cancer: From Diagnosis to Therapy. *Methods Mol Biol.* 1386:305-30.
- Chen JY, Shen QS, Zhou WZ, et al. (2015) Emergence, Retention and Selection: A Trilogy of Origination for Functional De Novo Proteins from Ancestral LncRNAs in Primates. *PLoS Genet.* 15;11(7):e1005391.
- Eloundou-Mbebi JM, Küken A, Omranian N, et al. (2016) A network property necessary for concentration robustness. *Nat Commun.* 19;7:13255.
- Vickovic S, Ståhl PL, Salmén F, et al. (2016) Massive and parallel expression profiling using microarrayed single-cell sequencing. *Nat Commun.* 14;7:13182.
- He F, Murabito E, Westerhoff HV. (2016) Synthetic biology and regulatory networks: where metabolic systems biology meets control engineering. *J R Soc Interface.* 13(117). pii: 20151046.
- Mestek Boukhibar L, Barkoulas M. (2016) The developmental genetics of biological robustness. *Ann Bot.* 117(5):699-707.
- Li S, Todor A, Luo R. (2015) Blood transcriptomics and metabolomics for personalized medicine. *Comput Struct Biotechnol J.* 31;14:1-7.
- Beck S, Lee BK, Kim J. (2014) Multi-layered global gene regulation in mouse embryonic stem cells. *Cell Mol Life Sci.* Sep 17. [Epub ahead of print]. DOI 10.1007/s00018-014-1734-9
- Wyles SP, Faustino RS, Li X, Terzic A, Nelson TJ. (2014) Systems-Based Technologies in Profiling the Stem Cell Molecular Framework for Cardioregenerative Medicine. *Stem Cell Rev.* Sep 14. [Epub ahead of print]. DOI 10.1007/s12015-014-9557-5
- Baslan T, Hicks J. (2014) Single cell sequencing approaches for complex biological systems. *Curr Opin Genet Dev.* 10;26C:59-65.
- Pathak RR, Davé V. (2014) Integrating omics technologies to study pulmonary physiology and pathology at the systems level. *Cell Physiol Biochem.* 33(5):1239-60.
- Conway O'Brien E, Prideaux S, Chevassut T. (2014) The epigenetic landscape of acute myeloid leukemia. *Adv Hematol.* 2014:103175.
- Schlichting CD, Wund MA (2014) Phenotypic plasticity and epigenetic marking: an assessment of evidence for genetic accommodation. *Evolution.* Mar;68(3):656-72.
- Wood JG, Helfand SL. (2013) Chromatin structure and transposable elements in organismal aging. *Front Genet.* 4;4:274.
- Mason CE, Porter SG, Smith TM. (2014) Characterizing multi-omic data in systems biology. *Adv Exp Med Biol.* 799:15-38.
- Rosa A, Brivanlou AH. (2013) Regulatory non-coding RNAs in pluripotent stem cells. *Int J Mol Sci.* 11;14(7):14346-73.

- Clarke J, Penas C, Pastori C, et al. (2013) Epigenetic pathways and glioblastoma treatment. *Epigenetics*. 8(8):785-95.
- Kyrtopoulos SA. (2013) Making sense of OMICS data in population-based environmental health studies. *Environ Mol Mutagen*. 54(7):468-79.
- Lovejoy DA, Barsyte-Lovejoy D. (2013) Systems approaches to genomic and epigenetic inter-regulation of peptide hormones in stress and reproduction. *Prog Biophys Mol Biol*. 113(3):375-86.
- Frebourg T. (2014) The challenge for the next generation of medical geneticists. *Hum Mutat*. 35(8):909-11.
- Georges A, Cambisano N, Ahariz N, Karim L, Georges M. (2013) A genome scan conducted in a multigenerational pedigree with convergent strabismus supports a complex genetic determinism. *PLoS One*. 23;8(12):e83574.
- Di Giulio M. (2013) The origin of the genetic code: matter of metabolism or physicochemical determinism? *J Mol Evol*. 77(4):131-3.
- Parrott R, Smith RA. (2014) Defining genes using "blueprint" versus "instruction" metaphors: effects for genetic determinism, response efficacy, and perceived control. *Health Commun*. 29(2):137-46.
- Yan Q. (2014) From pharmacogenomics and systems biology to personalized care: a framework of systems and dynamical medicine. *Methods Mol Biol*. 1175:3-17.
- Tobin AB, Prihandoko R. (2014) Reply to "Letter to the editor: 'Systems biology versus reductionism in cell physiology'". *Am J Physiol Cell Physiol*. 1;307(3):C310.
- Knepper MA, Raghuram V, Bradford D, et al. (2014) Letter to the editor: "Systems biology versus reductionism in cell physiology". *Am J Physiol Cell Physiol*. 1;307(3):C308-9.
- Winqvist RJ, Mullane K, Williams M. (2014) The fall and rise of pharmacology--(re-)defining the discipline? *Biochem Pharmacol*. 1;87(1):4-24.
- Bose B. (2013) Systems biology: a biologist's viewpoint. *Prog Biophys Mol Biol*. 113(3):358-68.
- Wolkenhauer O, Green S. (2013) The search for organizing principles as a cure against reductionism in systems medicine. *FEBS J*. 280(23):5938-48.
- Gare A. (2013) Overcoming the Newtonian paradigm: the unfinished project of theoretical biology from a Schellingian perspective. *Prog Biophys Mol Biol*. 113(1):5-24.
- Vogt H, Ulvestad E, Eriksen TE, Getz L. (2014) Getting personal: can systems medicine integrate scientific and humanistic conceptions of the patient? *J Eval Clin Pract*. Oct 14. doi: 10.1111/jep.12251. [Epub ahead of print]
- Westerhoff HV, Brooks AN, Simeonidis E, et al. (2014) Macromolecular networks and intelligence in microorganisms. *Front Microbiol*. 22;5:379.
- Werner HM, Mills GB, Ram PT. (2014) Cancer Systems Biology: a peek into the future of patient care? *Nat Rev Clin Oncol*. 11(3):167-76.
- Kompanichenko V. (2014) Emergence of biological organization through thermodynamic inversion. *Front Biosci (Elite Ed)*. 1;6:208-24.
- Goranson HT, Cardier B. (2013) A two-sorted logic for structurally modeling systems. *Prog Biophys Mol Biol*. 113(1):141-78.
- Fernandez-Leon JA. (2014) Robustness as a non-localizable relational phenomenon. *Biol Rev Camb Philos Soc*. 89(3):552-67.
- Gutiérrez J, Maere S. (2014) Modeling the evolution of molecular systems from a mechanistic perspective. *Trends Plant Sci*. 19(5):292-303.
- Goh T, Voß U, Farcot E, Bennett MJ, Bishopp A. (2014) Systems biology approaches to understand the role of auxin in root growth and development. *Physiol Plant*. 151(1):73-82.

- Agarwal S. (2013) Systems approaches in understanding evolution and evolvability. *Prog Biophys Mol Biol.* 113(3):369-74.
- Klinman JP, Kohen A. (2014) Evolutionary Aspects of Enzyme Dynamics. *J Biol Chem.* 31;289(44):30205-30212.
- Weinreich DM, Lan Y, Wylie CS, Heckendorn RB. (2013) Should evolutionary geneticists worry about higher-order epistasis? *Curr Opin Genet Dev.* 23(6):700-7.
- Barrick JE, Lenski RE. (2013) Genome dynamics during experimental evolution. *Nat Rev Genet.* 14(12):827-39.
- Soyer OS, O'Malley MA. (2013) Evolutionary systems biology: what it is and why it matters. *Bioessays.* 35(8):696-705.
- Burgess-Herbert SL, Euling SY. (2011) Use of comparative genomics approaches to characterize interspecies differences in response to environmental chemicals: challenges, opportunities, and research needs. *Toxicol Appl Pharmacol.* 15;271(3):372-85.
- Bolouri H. (2014) Modeling genomic regulatory networks with big data. *Trends Genet.* 30(5):182-91.
- Civelek M, Lusis AJ. (2014) Systems genetics approaches to understand complex traits. *Nat Rev Genet.* 15(1):34-48.
- Leiserson MD, Eldridge JV, Ramachandran S, Raphael BJ. (2013) Network analysis of GWAS data. *Curr Opin Genet Dev.* 23(6):602-10.
- Koo CL, Liew MJ, Mohamad MS, Salleh AH. (2013) A review for detecting gene-gene interactions using machine learning methods in genetic epidemiology. *Biomed Res Int.* 2013;2013:432375.
- Marjoram P, Zubair A, Nuzhdin SV. (2014) Post-GWAS: where next? More samples, more SNPs or more biology? *Heredity (Edinb).* 112(1):79-88.
- Murthy D, Attri KS, Gokhale RS. (2013) Network, nodes and nexus: systems approach to multitarget therapeutics. *Curr Opin Biotechnol.* 24(6):1129-36.
- Cull P. (2013) BIOCOMPUTATION: some history and prospects. *Biosystems.* 112(3):196-203.
- Pajoro A, Biewers S, Dougali E, et al. (2014) The (r)evolution of gene regulatory networks controlling Arabidopsis plant reproduction: a two-decade history. *J Exp Bot.* 65(17):4731-45.
- Najafi A, Bidkhori G, Bozorgmehr JH, Koch I, Masoudi-Nejad A. (2014) Genome scale modeling in systems biology: algorithms and resources. *Curr Genomics.* 15(2):130-59.
- Harrold JM, Ramanathan M, Mager DE. (2013) Network-based approaches in drug discovery and early development. *Clin Pharmacol Ther.* 94(6):651-8.
- Nilsson E, Zhang B, Skinner MK. (2013) Gene bionetworks that regulate ovarian primordial follicle assembly. *BMC Genomics.* 23;14:496.
- Antony PM, Balling R, Vlassis N. (2012) From systems biology to systems biomedicine. *Curr Opin Biotechnol.* 23(4):604-8.
- Hansen J, Iyengar R. (2013) Computation as the mechanistic bridge between precision medicine and systems therapeutics. *Clin Pharmacol Ther.* 93(1):117-28.
- Chalancon G, Ravarani CN, Balaji S, Martinez-Arias A, Aravind L, Jothi R, Babu MM. (2012) Interplay between gene expression noise and regulatory network architecture. *Trends Genet.* 28(5):221-32.
- He JC, Chuang PY, Ma'ayan A, Iyengar R (2012) Systems biology of kidney diseases. *Kidney Int.* 81(1):22-39.
- Chia NY, Ng HH. (2012) Stem cell genome-to-systems biology. *Wiley Interdiscip Rev Syst Biol Med.* 4(1):39-49.
- Zhao S, Iyengar R. (2012) Systems pharmacology: network analysis to identify multiscale mechanisms of drug action. *Annu Rev Pharmacol Toxicol.* 10;52:505-21.

- Antezana E, Mironov V, Kuiper M. (2012) The emergence of Semantic Systems Biology. *N Biotechnol.* 2012 Nov 16. [Epub ahead of print]
- Morelli LG, Uriu K, Ares S, Oates AC. (2012) Computational approaches to developmental patterning. *Science.* 13;336(6078):187-91
- Mitchell W, Matsumoto S. (2011) Large-scale integrated super-computing platform for next generation virtual drug discovery. *Curr Opin Chem Biol.* 15(4):553-9.
- Orchard S. (2012) Molecular interaction databases. *Proteomics.*12(10):1656-62.
- Hoyle RB, Avitabile D, Kierzek AM. (2012) Equation-free analysis of two-component system signalling model reveals the emergence of co-existing phenotypes in the absence of multistationarity. *PLoS Comput Biol.* 8(6):e1002396
- Borenstein E. (2012) Computational systems biology and in silico modeling of the human microbiome. *Brief Bioinform.* 2012 Nov;13(6):769-80.
- Aderem A. (2005) Systems biology: its practice and challenges. *Cell.*20;121(4):511-3.
- Hood L. (2003) Systems biology: integrating technology, biology, and computation. *Mech Ageing Dev.* 124(1):9-16.
- Hood L, Heath JR, Phelps ME, Lin B. (2004) Systems biology and new technologies enable predictive and preventative medicine. *Science.* 306(5696):640-3.
- Kirschner MW. (2005) The meaning of systems biology. *Cell.* 121(4):503-4.
- Kitano H. (2002) Systems biology: a brief overview. *Science.* 295(5560):1662-4.
- Kitano H. (2002) Computational systems biology. *Nature.* 14;420(6912):206-10.
- Kitano H. (2004) Biological robustness. *Nat Rev Genet.* 5(11):826-37.
- Kitano H. (2004) Cancer as a robust system: implications for anticancer therapy. *Nat Rev Cancer* 4(3):227-35.
- Kitano H. (2007) Towards a theory of biological robustness. *Mol Syst Biol.* 3:137.
- Lisacek, F. and Appel, R. D. (2007), *Systems Biology.* PROTEOMICS, 7: 825–827.
- Mihajlo Mesarovic, Sree N. Sreenath (2006) Beyond the Flat Earth Perspective in Systems Biology. *Biological Theory Winter.* Vol. 1, No. 1: 33–34.
- O'Malley MA, Dupré J. (2005) Fundamental issues in systems biology. *Bioessays* 27(12):1270-6.
- Sorger PK. (2005) A reductionist's systems biology: opinion. *Curr Opin Cell Biol.* 17(1):9-11.
- Soto AM, Sonnenschein C. (2004) The somatic mutation theory of cancer: growing problems with the paradigm? *Bioessays.* 26(10):1097-107.
- Westerhoff HV, Palsson BO. (2004) The evolution of molecular biology into systems biology. *Nat Biotechnol.* 22(10):1249-52.
- Sneppen K, Krishna S, Semsey S. (2010) Simplified models of biological networks. *Annu Rev Biophys.* 9;39:43-59.
- Gavin AC, Maeda K, Kühner S. (2010) Recent advances in charting protein-protein interaction: mass spectrometry-based approaches. *Curr Opin Biotechnol.* Oct 8. [Epub ahead of print].
- Little JW. (2010) Evolution of complex gene regulatory circuits by addition of refinements. *Curr Biol.* 14;20(17):R724-34.
- Maly IV. (2009) Introduction: a practical guide to the systems approach in biology. *Methods Mol Biol.* 500:3-13.

## Letter to the editor: “Systems biology versus reductionism in cell physiology”

**Mark A. Knepper, Viswanathan Raghuram, Davis Bradford, Chung-Lin Chou, Jason D. Hoffert, and Trairak Pisitkun**

*Epithelial Systems Biology Laboratory, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland*

TO THE EDITOR: The following is a response to the editorial comment of Prihandoko and Tobin (15) about our recent paper in *American Journal of Physiology-Cell Physiology* (2), which addresses a key question in modeling of signaling networks: How to assign the protein kinases (from the entire 521-member kinome list) that are responsible for each measurable phosphorylation event in a given cell type. In our study, we used vasopressin-stimulated phosphorylation of the water channel protein, aquaporin-2, at serine-256 as an example because of its importance to the physiology of collecting duct principal cells. We thank Prihandoko and Tobin for their thorough and well thought out summary of our paper. We write now to provide additional clarification regarding the epistemological approach, which was based on a systems biological framework rather than on reductionist principles. Understanding the two ways of doing experiments is aided by a bit of history.

Attention to the problem of how to make practical scientific inferences from scientific observations peaked in 19th century with John Stuart Mill's book “*A System of Logic*” (12; see chapter “Of the Four Methods of Scientific Inquiry”). Mill's work described several approaches built from two fundamental methods, viz. the “method of difference” and the “method of agreement.” From the viewpoint of modern biology, the former method is the basis of reductionist approaches and became dominant in the 20th century. The latter method is the basis of the newly resurgent systems biology approach. We can conceptualize the method of difference as the standard hypothesis-driven experiment in which a given variable is altered and another variable is observed. This approach thrived because it has often been feasible to make the targeted measurements needed and because statistical methods were developed early in the 20th century by Fisher and others to analyze such data (14). However, reductionist approaches have drawn fire in recent years because of perceived bias in publication (7). Critics claim that positive results from reductionist experiments are publishable (often whether true-positive or false-positive), while negative results are not. In addition, the statistical approach to analysis of reductionist data draws conclusions one experiment at a time, and does not generally utilize prior information to draw conclusions (4, 14), a problem that is circumvented in systems biological approaches. The latter, roughly equivalent to Mill's method of agreement, looks broadly for correlations in comprehensive data sets and builds models based on these correlations. Comprehensive methodologies including large-scale proteomics, DNA microarrays, and “next generation” DNA sequencing have only recently become feasible because of the availability of genome-wide sequence data needed for mapping. Thus, biological approaches based on Mill's method of agreement

(systems biology approaches), heretofore impractical, have in the 21st century become feasible. Concomitantly, statistical methodologies for analysis of comprehensive data sets have followed, e.g., the use of Bayesian statistics. Our study (2) utilized the systems approach as summarized in the next two paragraphs. The commentary (15) appeared to retell the story that we presented as a series of separately interpreted reductionist experiments, thus losing the major message of our paper, viz. that Bayes' theorem can be used to integrate multiple imperfect data sets to provide deeper, stronger conclusions than could be expected without data integration.

Our previous study in *AJP-Cell* (5) showed, using mass spectrometry, that protein kinases are low fidelity enzymes and when combined with prior observations (11) suggested that protein kinases gain specificity in the cell chiefly through factors that cause them to colocalize with specific substrates. From this and other studies, it was already clear that we can rely only on very general specificity constraints, basically whether they phosphorylate tyrosines or serines/theonines, and whether the latter are basophilic, acidophilic, or proline-directed. Thus, the question of what protein kinase(s) phosphorylate serine-256 of aquaporin-2 was not answerable simply by looking at the amino acid sequence surrounding it. More information was needed. To address the question, we integrated prior information from several sources using Bayes' theorem to rank all 521 kinases in the rat genome with regard to the probability that they phosphorylate serine-256 of aquaporin-2 in the rat inner medullary collecting duct (IMCD). This included data gleaned from prior large-scale (proteomic or transcriptomic) experiments in the IMCD. This Bayes' approach allowed us to utilize data, which in isolation did not answer the question, but narrowed the choices. For example, transcriptomics experiments divided the 521 protein kinase genes into those that were expressed in IMCD and those that were not detectable, and thus were unlikely to play a regulatory role regardless of kinase specificity. Use of Bayes' theorem to integrate information from many sources is not new; it was used for example to establish the conclusion that smoking is harmful to health in the 1950s (3). However, as far as we can tell, the use of Bayes' theorem to integrate multiple data sets in cell physiology is novel and it is therefore surprising that it was not explicitly discussed in the Prihandoko and Tobin commentary.

Using the Bayesian integration of prior data as a launching point, our study (2) addressed whether addition of inhibitor data could sharpen the Bayesian estimates. Protein kinase inhibitors have been used in physiology for many decades, always with tacit recognition that they inhibit multiple kinases in addition to the nominal target kinase. Now, the International Centre for Kinase Profiling (ICKP, <http://www.kinase-screen.mrc.ac.uk/kinase-inhibitors>) has provided profiling data for many commonly used protein kinase inhibitors. This comprehensive

Address for reprint requests and other correspondence: M. A. Knepper, National Institutes of Health, Bldg. 10, Rm. 6N307, 10 Center Dr., MSC-1603, Bethesda, MD 20892-1603 (e-mail: [knepper@nhlbi.nih.gov](mailto:knepper@nhlbi.nih.gov)).

data set identifies which kinases are and which kinases are not inhibited by a given small-molecule kinase inhibitor, and estimates the percentage of kinase activity remaining for relevant inhibitor concentrations. The ICKP data give new life to the use of inhibitors in physiological experiments by its comprehensive nature. It allowed phosphorylation data from immunoblotting of IMCD suspensions to be integrated with prior data using Bayes' theorem, thereby significantly improving discrimination among candidate kinases involved in aquaporin-2 phosphorylation at serine-256. The overall Bayes' analysis shows that the conventional wisdom, that protein kinase A phosphorylates this site in the collecting duct cell, is not any better supported by the data than roles for several other basophilic protein kinases including calcium/calmodulin-dependent protein kinase 2 $\delta$  (Camk2d) and protein kinase B- $\alpha$  (Akt1). In fact, the top ranked protein kinase in the Bayes' analysis, calcium/calmodulin-dependent protein kinase 2 $\delta$ , was shown in mass spectrometry experiments to be as potent in phosphorylating aquaporin-2 in vitro as was protein kinase A, or more so.

In summary, our paper used a systems biological approach involving application of Bayes' theorem to integrate multiple data sets. Such an approach appears to be new to cell physiology and appears to provide significant advantages for certain physiological problems such as the assignment of kinases to phosphorylation sites. We as authors recognize that the onus is on us to provide a persuasive argument for the systems approach. It may indeed be difficult for many biologists to embrace systems biology after a 100 years of reductionism. Toward that end, we invite the interested reader to view our previous writings about systems biology in *AJP-Cell* (8, 9) as well as recent articles by others in this journal (1, 6, 10, 13, 16).

#### ACKNOWLEDGMENTS

Present address of T. Pisitkun: Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Supported by NHLBI Division of Intramural Research (Project Z01-HL-001285).

#### DISCLOSURES

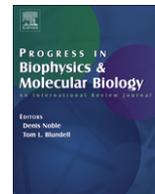
No conflicts of interest, financial or otherwise, are declared by the author(s).

#### AUTHOR CONTRIBUTIONS

M.A.K. drafted manuscript; M.A.K., V.R., D.B., C.-L.C., J.D.H., and T.P. edited and revised manuscript; M.A.K., V.R., D.B., C.-L.C., J.D.H., and T.P. approved final version of manuscript.

#### REFERENCES

1. Beard DA, Vendelin M. Systems biology of the mitochondrion. *Am J Physiol Cell Physiol* 291: C1101–C1103, 2006.
2. Bradford D, Raghuram V, Wilson JL, Chou CL, Hoffert JD, Knepper MA, Pisitkun T. Use of LC-MS/MS and Bayes' theorem to identify protein kinases that phosphorylate aquaporin-2 at Ser<sup>256</sup>. *Am J Physiol Cell Physiol* 307: C123–C139, 2014.
3. Cornfield J, Haehszel W, Hammond EC, Lilienfield AM, Shimkin MB, Wynder EL. Smoking and lung cancer: recent evidence and a discussion of some questions. *J Natl Cancer Inst* 22: 173–203, 1959.
4. Davidoff F. Standing statistics right side up. *Ann Intern Med* 130: 1019–1021, 1999.
5. Douglass J, Gunaratne R, Bradford D, Saeed F, Hoffert JD, Steinbach PJ, Knepper MA, Pisitkun T. Identifying protein kinase target preferences using mass spectrometry. *Am J Physiol Cell Physiol* 303: C715–C727, 2012.
6. George CH, Parthimos D, Silvester NC. A network-oriented perspective on cardiac calcium signaling. *Am J Physiol Cell Physiol* 303: C897–C910, 2012.
7. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2: e124, 2005.
8. Knepper MA. Systems biology in physiology: the vasopressin signaling network in kidney. *Am J Physiol Cell Physiol* 303: C1115–C1124, 2012.
9. Knepper MA. Proteomic pearl diving versus systems biology in cell physiology. Focus on "Proteomic mapping of proteins released during necrosis and apoptosis from cultured neonatal cardiac myocytes." *Am J Physiol Cell Physiol* 306: C634–C635, 2014.
10. Kohli P, Bartram MP, Habbig S, Pahmeyer C, Lamkemeyer T, Benzing T, Schermer B, Rinschen MM. Label-free quantitative proteomic analysis of the YAP/TAZ interactome. *Am J Physiol Cell Physiol* 306: C805–C818, 2014.
11. Linding R, Jensen LJ, Ostheimer GJ, van Vugt MA, Jorgensen C, Miron IM, Diella F, Colwill K, Taylor L, Elder K, Metalnikov P, Nguyen V, Pasculescu A, Jin J, Park JG, Samson LD, Woodgett JR, Russell RB, Bork P, Yaffe MB, Pawson T. Systematic discovery of in vivo phosphorylation networks. *Cell* 129: 1415–1426, 2007.
12. Mill JS. *A System of Logic: Ratiocinative and Inductive*. Honolulu: University Press of the Pacific, 1891.
13. Moore NM, Nagahara LA. Physical Biology in Cancer. 1. Cellular physics of cancer metastasis. *Am J Physiol Cell Physiol* 306: C78–C79, 2014.
14. Nuzzo R. Scientific method: statistical errors. *Nature* 506: 150–152, 2014.
15. Prihandoko R, Tobin AB. Challenges of assigning protein kinases to in vivo phosphorylation events. Focus on "Use of LC-MS/MS and Bayes' theorem to identify protein kinases that phosphorylate aquaporin-2 at Ser<sup>256</sup>." *Am J Physiol Cell Physiol* 307: C121–C122, 2014.
16. Welch GR, Clegg JS. From protoplasmic theory to cellular systems biology: a 150-year reflection. *Am J Physiol Cell Physiol* 298: C1280–C1290, 2010.



## Original research

## Chance between holism and reductionism: Tensions in the conceptualisation of Life

Charles T. Wolfe\*

Centre for History of Science, Department of Philosophy and Moral Sciences, University of Ghent, Blandijnberg 2, B-9000 Ghent, Belgium

## ARTICLE INFO

Article history:  
Available online 18 May 2012

Keywords:  
Chance  
Reductionism  
Holism  
Organicism  
Jean-Jacques Kupiec

## ABSTRACT

In debates between holism and reductionism in biology, from the early twentieth century to more recent re-enactments involving genetic reductionism, developmental systems theory or systems biology, the role of chance – the presence of theories invoking chance as a strong explanatory principle – is hardly ever acknowledged. Conversely, Darwinian models of chance and selection (Dennett, 1995; Kupiec, 1996, 2009) sit awkwardly with reductionist and holistic concepts, which they alternately challenge or approve of. I suggest that the juxtaposition of chance and the holism–reductionism pair (at multiple levels, ontological and methodological, pertaining to the vision of scientific practice as well as to the foundations of a vision of Nature, implicit or explicit) allows the theorist to shed some new light on these perennial tensions in the conceptualisation of Life.

© 2012 Elsevier Ltd. All rights reserved.

Interest shifts...from an intelligence that shaped things once for all to the particular intelligences which things are even now shaping (Dewey, 1910/2007, p. 10)

## 1. Introduction

The juxtaposition of chance with the more familiar pair of holism and reductionism in biology may at first sight seem rather surprising. Chance is both an ancient philosophical problem, as addressed – quite differently – by Aristotle, Lucretius or Diderot (Gigandet, 2002; Wolfe, 2010c; Pépin, 2012); a concept closely linked to the emergence of ‘modern’ biology, from Darwin to the study of genetic mutations; today it is discussed in a new way on both the experimental and theoretical planes, particularly in the more manipulable form of stochasticity (Kupiec et al., 2009/2011; Kupiec, 2010). Holism is a term that always carries with it a residual dimension of mystery, referring initially to a set of positions that goes back to Aristotle and Hegel, then – most relevantly for our topic here – to a position in theoretical biology inspired by general systems theory (Smuts, 1926/1999; Ash, 1995); in a more existential sense, it is also associated with the ‘organicism’ of Kurt Goldstein (Goldstein, 1995). Holism has also been revived more recently in analytic philosophy with Robert Brandom and John McDowell (for recent analyses of holism in metaphysics, philosophy of mind and

the philosophy of language see Esfeld, 1999 and Block, 1998). But for our purposes ‘holism’ is a certain type of claim about how specifically living beings – organisms overall, but particularly live ones – should be considered as *wholes*, even if there is no rigorous, clear-cut distinction or relation between holism, systems theory and specifically organismic claims about the uniqueness of living beings.<sup>1</sup>

Briefly put, models appealing to chance are (philosophically) *anti-essentialist*: they reject the appeal to higher-level, irreducible properties of a system by retracing the causal process which generated them, based on stochastic processes. It seems intuitively right – and empirically indeed to be the case – that models favouring the role of chance tend to be compatible with reduction, or *reductionism* as an ontological and/or explanatory position according to which for any given Whole there will always be

<sup>1</sup> The ‘classic’ authors Smuts, von Neumann and von Bertalanffy all waver in between statements of holism as a total systemic standpoint (with no particular reference to a special status for living entities) and holism as an approach or model which sheds particular light on embryology and how organisms are not mere machines (with reference to teleology and the ‘historical’ or ‘learned’ character of organisms). These authors also specify abstract terms on which ‘merely mechanical aggregates’ are different from genuine wholes, including chemical compounds, and then suddenly specify that biological organisms are the exemplars of “creative wholes,” as Smuts calls them (wholes which create structures different from their constituents or parts) (Smuts, 1926/1999, pp. 140–141). The best general discussion of holism in early twentieth-century science is Ash (1995). See also Peterson (2010), which is forthcoming in book form from Springer (Series in History, Philosophy and Theory of the Life Sciences).

\* Tel.: +32 9264 3952; fax: +32 9264 4187.

E-mail addresses: [charles.wolfe@ugent.be](mailto:charles.wolfe@ugent.be), [ctwolfe1@gmail.com](mailto:ctwolfe1@gmail.com).

subadjacent components which themselves can explain, with or without 'bonuses' such as bridge laws or structural features, the overall function of this Whole. But little attention has been paid to this relation between chance, anti-essentialism and reduction.

For instance, a Darwinian model of chance and selection (Dennett, 1995; Kupiec, 1996) seems to be in conflict with a systemic holism as put forth in Varela and his partisans (Weber and Varela, 2002; Rudrauf et al., 2003), who tend to insist on the irreducible individuality of systems (or worse, a metaphysics of Life) rather than their production through stochastic processes, or similarly in their insistence on the existence of a foundational centre or Self in living systems (Wolfe, 2010b). In contrast, this postulate seems absent from the work of Moreno and his collaborators (Ruiz-Mirazo et al., 2000), which shows that it is possible to articulate an organisational – and hence weakly holistic – model without adjoining it to the individualism or anti-Darwinism of a Varela (Bechtel, 2007). I suggest that the juxtaposition of chance with the holism–reductionism pair (at multiple levels, ontological and methodological, pertaining to the vision of scientific practice as well as to the foundations of a vision of Nature, implicit or explicit) allows the theorist to shed some new light on these perennial tensions in the conceptualisation of Life.

## 2.

When we think of the role of chance in biology – the presence of chance, or more restrictively, 'stochastic processes' as productive in biology (and I leave aside the question, 'productive of what?' – of order? of particular organisms? of structures enabling the generation of organisms? – in order to merely stress: the idea that a chance and selection model is *productive*) we often think of Darwin. We can augment his ideas of variation and natural selection (in which chance plays the role of producing what sort of variation will occur in organisms living in a given environment, on which natural selection will then act) with later developments such as random mutations, genetic drift – the idea that most genetic variation we observe at the molecular level is not to be accounted for in terms of selection, but rather as a consequence of mutation and (random) genetic drift, in which the fixation of genes in populations is a purely stochastic process (Kimura, 1983), etc. At that point one will typically enter into a 'more or less' discussion: is a particular factor decisive or not? Are its effects real or apparent? How many of these effects make a cause *the cause* of a phenomenon? But if we consider instead the attitudes towards the concept of chance within a schematic summary of the history of philosophy, in addition to debates about whether the world is the product of necessity or chance (with a predominant denial that chance can serve as any sort of explanatory factor, paradigmatically in Aristotle<sup>2</sup>), we find a different feature: a distinctly *radical* dimension of chance. The latter attitude is radical in the sense that it is destructive or at least deflationary: it says, 'show me a complex phenomenon A and I will show you how chance/variation-and-selection/stochastic processes B have produced it'.

Thinkers such as Lucretius, Diderot, more recently Daniel Dennett and – centrally to this essay – Jean-Jacques Kupiec have actively insisted on the role of chance or a fundamental randomness at the heart of nature, as either 'productive of order' or in any

case a more basic, 'genuine' level of reality than the perceived forms and species of our experience. Conversely, numerous other thinkers of some eminence (Aristotle and Kant come to mind) have warned against the dangers of a theory which grants such a productive and fundamental role to chance, in the name of the stability or integrity of Forms, of the organism (as in Hans Jonas, e.g. Jonas, 1966, pp. 74–92) or of the person: if, so these thinkers argue, we open the door to explanations by chance, then none of the entities we depend on for a meaningful life can remain. In all cases here, what is at issue is chance as a feature of the world, not as a feature of our knowledge conditions (as in unpredictability or novelty understood as epistemological categories). What happens if we try and confront these aspects of the history of philosophy, with some key moments in theoretical biology? The confrontation reveals a certain instability or, differently put, a degree of conceptual incommensurability. That is, the introduction of chance renders the traditional opposition between holism and reductionism more unstable – less clear-cut.

We are familiar with various forms of this opposition, particularly, as regards the present context, that between holism as the insistence on the irreducible organizational dimension of systems (whether in the sense of autopoiesis, the more recent Developmental Systems Theory or DST, as in Oyama, 1985/2000, or the role of development which 'trumps' reductive genetic explanations), and reductionism as a series of factually rather distinct possible claims: that 'you are your biochemistry' (Loeb, 1912), that one should focus on reduction towards the *molecular* level (molecular biology or cellular neuroscience rather than cognitive neuroscience, Bickle, 2006) or towards the *genetic* level (Monod, Dawkins, Dennett, etc.). But it should be clear that in fact they are not logical opposites; the opposition is less monolithic than it seems. Even a classic of genetic reductionism like Monod can move within one sentence from proclaiming genetic reductionism, "Thus defined, the theory of the genetic code is the fundamental basis of biology" to a much more flexible position, with anti-determinist or at least non-determinist tones: "this does not mean, of course, that the complex structures and functions of organisms can be deduced from [the theory of the genetic code], nor even that they are always directly analysable on the molecular level" (Monod, 1970, p. 12; Monod, 1971, p. xii). Again, there is no real contradiction here, especially if we consider that there is a difference between the claim of genetic *determinism* and that of genetic *reductionism*: the latter is a more flexible claim. As Gayon suggests, genetic reductionism "does not claim that genes wholly *determine* the genesis of organismic traits, but that the explanation of these traits must significantly include genetic factors." On this view, "the best explanation of a biological trait is that which specifies the way in which genes determine this trait in a given organismic and environmental context" (Gayon, 2009/2011, p. 81/117). Reduction here is neither a strict ontological claim about what is real and what should be eliminated from our vision of Nature nor a strict nomological claim about inter-theoretic reduction between sets of laws. It is, Gayon suggests, more of a heuristic claim about how to account for a biological phenomenon.

Conversely, organisational models are not adverse to defining the systems that compose the organisational wholes in which they are interested, in a mechanistic fashion (whether or not this is overtly reductionist; Bickle, 2006, p. 430; Bechtel, 2007, p. 270). That is, organisational models essentially articulate together key insights from mechanistic science and the holistic or 'organismic' critiques of mechanism. More precisely, they combine the mechanistic explanatory programme to study (by reduction, modelling and componential analysis) the structures at work in organisms and the organicist (holist) standpoint which minimally "remind[s] mechanists of the shortfalls of the mechanistic accounts on offer," for ideas such as "negative feedback, self-organising positive feedback and

<sup>2</sup> To give just one example, when Aristotle discusses how it is that organisms come to be as organised, stable wholes, he clearly states, "organic development is either for the sake of something [i.e. according to a final cause, CW] or by chance; it is not by chance (since chance outcomes are irregular whereas organic outcomes regular); therefore organic development is for the sake of something" (Aristotle, 1984, II.8, 198b34–199b7).

cyclic organisation are critical to explaining the phenomena exhibited by living organisms” (Bechtel, 2007, pp. 296–297). Differently put, “*system thinking* does not imply forgetting about the material mechanisms that are crucial to trigger off a biological type of phenomenon/behaviour; rather, it means putting the emphasis on the interactive processes that make it up, that is, on the dynamic organization in which biomolecules (or, rather, their precursors) actually get integrated” (Ruiz-Mirazo and Moreno, 2004, p. 238).

But what of chance? It enables us to move away from the constant back-and-forth between reductionist models and more holistic models (strict genetic inheritance versus ecological inheritance, selfish genes versus organisms, genomics versus Evo-Devo and so on), in a kind of ‘triangulation’. What Kupiec called ‘cellular Darwinism’ and now more expansively is calling ‘ontophylogenesis’ (a term somewhat reminiscent of Buss, 1987, who also felt that evolutionary accounts of phylogenesis needed to be supplemented with accounts of ontogenesis, the emergence of individuals; Kupiec’s idea is to be more Darwinian than Darwin, and explain, not just the origin of *species* but the origin of *individuals* through variation and selection; see summary in Laplane, 2011) is as different from classic genetic reductionism as it is from the classic anti-reductionist positions which he suspects are too holistic (using the term in a more pejorative sense to mean views which are insufficiently grounded in experimental science). Indeed, instead of treating them as binary opposites, Kupiec finds these positions to be complementary types of mistakes:

Since genetic determinism is reductionist, holism would at first sight seem to be incompatible with it. Nevertheless, the two concepts unite in affirming the objective reality of order. In both cases a first principle is involved which structures the world and directs processes. In genetic determinism, the principle of order from order comes into play through the stereospecificity of the molecules, while in holism, the creative principle, less well defined and with a variety of names, creates organised wholes (Kupiec, 2009, p. 77).

I’ll return in closing to the challenge presented here towards any strong notion of order, but for now wish to focus more on where this view fits in relation to these ‘mistaken positions’ it challenges.

### 3.

Curiously, if we map out these positions in theoretical biology, they bear a striking resemblance to the landscape in contemporary moral philosophy – specifically regarding freedom versus determinism. A brief comparison should make this obvious. In analytic philosophy, the basic positions in the debate over whether we are free agents or simple parts of a deterministic universe, are usually presented as follows (with each of these obviously coming in different forms, weak or strong, pure or hybrid, etc.):

A: *libertarianism* (not to be confused with the political or economic doctrines which bear this name). Morally, this is the view that we are absolutely free, that agents respond to reasons, not causes, and are self-governing (rather than influenced by their genes, their environment or what they had for breakfast). The libertarian may or may not accept that Nature is governed by causal processes, but she asserts that our existence as moral agents has nothing to do with these forms of causality. Biologically, this corresponds to a view found in German Idealist philosophy of nature (e.g. Hegel’s), but also in Hans Jonas, in Varela and other thinkers calling either for a return to Aristotelianism or to a Romantic conception of Nature. They believe that ‘Life’ is entirely separate from physical science. There may or may not be a possible science of life on this view, but if there

is, it will not resemble the science of Monod and Jacob but rather that of Driesch, the Baldwin effect and Margulis. Sometimes, however, these take the form of a more sophisticated, less metaphysically laden view which is still a form of organicism, without necessarily being what Monod and Kupiec call ‘animism’: for instance, the distinguished theorist of developmental systems, Susan Oyama, speaks of “the organism as layered vital reality,” and insists on “the organism as a locus of agency” (Oyama, 1985/2000, p. 162, 2000, p. 95).<sup>3</sup>

- B: *determinism* is the most straightforward case here, in morals as in biological thought. It is the idea, whether or not we take it in its specifically Laplacian form, that there is a kind of grid on which all things are located (or more metaphysically, a grid including all future possibilities), such that causal, or mechanical, or atomic concepts exhaustively account for the behaviour of all such entities. Morally, it is the absolute opposite of the idea of freedom in the sense that I am the originator of my actions; scientifically, it supports the idea that there are absolute correspondences, whether between genes and behaviour, or laws of physics, etc. In early modern thought, when Hobbes claims that everything is matter and motion, including the thoughts in my head, this is a ‘necessitarian’ (determinist) view. Biologically, the most pure statement of determinism is to say that the phenotype is the expression of the genotype.
- C: *compatibilism* is the most complex and the most interesting position, both in moral thought, where it involves recognising a degree of determinism while also arguing that we have what Dennett called some ‘elbow room’ within a deterministic universe. Spinoza’s idea that the more I come to be aware of the causal processes within me and without me, the freer I am, is a compatibilist idea. The idea that I am governed by my beliefs, desires and conditioning rather than strictly by laws of physics (a view held by Hume, Moritz Schlick and A.J. Ayer amongst others) is a compatibilist idea. What is the analogue to compatibilism in the biological sphere? Precisely, the anti-essentialist privileging of chance (Lucretius, Diderot, Darwin, Dewey, Kupiec), which recognises the existence of causality without defending causal *fundamentalism* (a pluralism of causes, then). Indeed, to the criticism which might say, if we simply replace traditional essences by another concept called ‘chance’, aren’t we still being essentialists?, one can reply that in both Darwin and Kupiec, chance, variation and selection are all factors<sup>4</sup>:

Each cell, although working for its own good, is subordinate to the whole. It does not enjoy total freedom as its freedom is limited in that the cell is constrained to differentiate in a way appropriate to the place it occupies in the society of cells (Kupiec, 2009, p. 124)

And of course if we think back to Claude Bernard, who popularized the term ‘determinism’ in the first place (Gayon, 2009/2011; Pépin, 2012), the relation is actually stronger than one of analogy, for Bernard makes a literal usage of ‘freedom’ and ‘determinism’ as descriptions both of biological entities and of methodological rules for dealing with such entities (Bernard, 1865/1927, Part II, chapter II). Like Jacques Loeb in the early twentieth century, Bernard seeks

<sup>3</sup> Elementary fairness leads me to specify that Oyama herself explicitly states that her position weakens the postulate common to what she calls – in a partly meta-historical way – preformationism and epigenesis, namely, the postulate that matter cannot acquire a biological form without there being an external source of this form. But it seems more interesting to me to present the tensions between ‘sophisticated’, nuanced theorists than between caricatural, dogmatic ones.

<sup>4</sup> However, Kupiec approvingly cites the neural Darwinism of Changeux, then Edelman, which precisely seems to make the mistake of re-essentialising Darwinism as an explanatory principle (Kupiec, 2009, p. 106).

to give analytic, mechanistic accounts of living systems while at the same time doing justice to their integrative features. But with respect to anti-essentialism, the idea is that position (C), which in moral philosophy would be compatibilism, here in biological theory amounts to the rejection both of genocentric essentialism and of holistic, systemic essentialism.

#### 4.

This anti-essentialism entails, or rather is expressed crucially in the fact that, notably unlike Schrödinger in *What is Life?* (to name a famous, and perhaps foundational example; Schrödinger, 1944), Kupiec does not recognise the existence of something like a *program*; “Because of the stochastic nature of protein interaction and gene expression, [Kupiec] says, there can be no Aristotelian form or programme to give order to life and ward off entropic chaos and death” (Werner, 2009, p. 35). Overall, the argument founded on chance and selection is anti-essentialist *per definitionem* because the primacy of chance over structure is the exact opposite of the Aristotelian insistence on the primacy of form over matter (Kupiec, 1999). Evolution is not an essentialist business, for species are populational constructs (and organisms are not essence either, Wolfe, 2010b). On a more pragmatic level, we can say with Ereshefsky that “Positing biological essences does not illuminate biological practice nor does it help us understand how science works” (Ereshefsky, 2010, p. 684). But Kupiec’s claim is stronger:

modern biology is still impregnated with pre-scientific essentialism, hindering its development. This essentialism presents the Form as the prime entity and one that it seems impossible to go beyond, and gives rise to the contradiction in genetic determinism. We shall see that this impasse originates in the belief we have in the reality of the species. We are blinded by what seems absolutely obvious, and this leads us to see the species as the insurmountable horizon of biological thought (Kupiec, 2009, p. 177).

And this puts us on a metaphysical plane, which enables me to relate Kupiec’s ‘Darwinian’ anti-essentialism to a more strictly philosophical cousin, Althusser’s ‘Lucretian’ anti-essentialism. If Lucretius believed that the world was made up of atoms and their random swerves (*clinamen*) – which introduces a dimension of chance into what was otherwise a fairly static view of atomism – the late Althusser, in his posthumously published writings, speaks of a “materialism of the encounter,” where the latter term refers to the sudden ‘encounter’ between atoms originally described by Epicurus and Lucretius:

the encounter doesn’t create any of the reality of the world, which is nothing but agglomerated atoms, but it grants reality to the atoms themselves, which without the deviation and encounter would be nothing but abstract elements, without any tangible existence. The atoms’ very existence is dependent on the deviation and the encounter (Althusser, 1994, pp. 541–542).<sup>5</sup>

There are no essences here, no Platonic forms or first principles like Aristotle’s *noûs* (‘mind’ or ‘intellect’) which is prior to all contingent natural forms: “since nothing which is accidental is prior to what is *per se*, it is clear that no accidental cause can be prior to a cause *per se*. Spontaneity and chance, therefore, are posterior to *noûs* and nature” (Aristotle, 1984, II.6, 198a7–10); there are encounters and their effects.

But the specifically biological anti-essentialism also makes a different point: that information itself is a kind of essence. Here

the criticism is quite similar to that of, e.g. Susan Oyama, who writes that “when atheistic evolutionists deify information they seem to lack the courage of their materialist convictions” (Oyama, 2009, p. 43). But if we recall my distinction between the three basic positions A, B and C, Oyama’s critique of the informational model of the gene belonged to (A), which opposed the intrinsic features of living beings to the ‘disembodied’ character of information (a criticism of a view as *disembodied* means the position argued for belongs to the family of theories defending ‘embodiment’, as discussed e.g. in Shapiro, 2007). In contrast, ‘cellular Darwinism’ makes no claims about the uniqueness of organisms faced with the rest of the physical world.

Granted, not all the criticisms of ‘disembodiment’ belong to that shopworn category, ‘mysterious vitalism’ (while in any case vitalism exists and has existed in far more varied forms than biologists or philosophers of biology ever seem to notice; Oyama, 2010; Wolfe, 2011). That is, Oyama and others can state that the obsession with information theory dating back to Schrödinger leads people to lose sight of key features of, say, development, without this statement at all invoking mysterious, extra-causal forces like entelechies – although a prominent theorist of embodiment and former collaborator of Varela’s, Evan Thompson, does reintroduce the metaphysical *crispation* that one might have hoped to have dispensed with, when he argues that “Life is not physical in the standard materialist sense of purely external structure and function. Life realises a kind of interiority, the interiority of selfhood and sense-making” (Thompson, 2007, p. 238). But Kupiec’s criticism is different. When he criticises genetics for its vision of ontogenesis as a unidirectional process leading from DNA to the phenotype (the expression of genetic information), he does so *in the name of Darwinism*, in that sense challenging the integrity of the Modern Synthesis (Kupiec and Sonigo, 2000, p. 88; Schaeffer, 2007, p. 173).

Both Darwin and Claude Bernard are inspirations for this anti-essentialist attitude towards the status of biological entities, which are *de-substantialized* here (as discussed in the ‘five arguments’ which open Chapter 2 of Kupiec, 2009) or *processualized*; Bernard often insisted that the novel properties he was describing (ultimately the *milieu intérieur* or what we have come to call homeostasis) were not the properties of a special kind of substance (which would have been vitalism, in his view) but rather were properties of certain kinds of *relations* (Bernard, 1865/1927, p. 66). In contemporary biology and close to Kupiec, a key moment was Lewontin’s work, in which the organism becomes a *porte-manteau* concept, a place-holder in between gene, population and ecosystem (which themselves are strictly processual concepts as well); there is no privileging of any particular unit of selection as more ‘real’ or ‘irreducible’ than any other, in a selection process which involves nothing other than phenotypic variation, differential phenotypic fitnesses (depending on environments), and the heritability of fitness (Lewontin, 1970, p. 1); “just as there is no organism without an environment, so there is no environment without an organism” (Lewontin, 1983/1985, p. 99).

Because after all if we maintain, on a substantialist view, that organisms are something special – *norganisms*, in Julian Huxley’s ironic phrase describing Haldane’s reaction to his own mechanist views<sup>6</sup> – we are guilty, or may be guilty, of “spiritualising matter,” to borrow an expression from the eighteenth-century materialist philosopher La Mettrie – this mistake being akin to what Kupiec

<sup>5</sup> For English translations see Althusser (2006), and for extensive commentary see Bourdin (2005).

<sup>6</sup> “Dr. Haldane called himself an organicist, which implied being anti-mechanist and yet not a mystic vitalist – I never quite grasped what he really meant. At any rate it led to some passages at arms. As I was describing some experiment which demanded a mechanistic explanation, he burst out with ‘But it’s a *norganism*, my dear young fellow, a *norganism*!’” (Huxley, 1971, p. 138).

calls 'animism'. In the first pages of his notorious work *L'Homme-Machine*, La Mettrie charged that Leibnizians "with their *Monads*,... have spiritualised matter rather than materialising the soul" (de La Mettrie, 1748/1960, p. 149), the irony being that precisely some of these versions of the Leibnizian monads, turned into 'molecules' or 'seeds of matter', in fact became, notably in Maupertuis, early theories of genetic information (Wolfe, 2010a). Animism, spiritualising matter, mysterious embodiment: all of these are more or less identified in Kupiec's deflationary, Darwinian perspective which, as I shall discuss in closing, puts him closer to the reductionist standpoint.

## 5.

I suggested earlier that my proposed triangulation between holism, reductionism and chance produces some curious effects. Indeed, from Lucretius to Diderot, Darwin and Tyndall<sup>7</sup> and onto Dennett and Kupiec, the type of biological theory that asserts the primacy of chance is *reductionist* in the sense that it rejects the existence of all irreducible totalities (including notions of design and order), *without* however being identical with classic forms of reductionism – which are historically diverse: Cartesian mechanism, biochemically inspired 'vulgar materialism' in the nineteenth century (Vogt, Büchner) or the revival of atomism, as stated for instance by Emil Du Bois-Reymond:

Natural science – or, more definitely, knowledge of the physical world with the aid of and in the sense of theoretical natural science – means the reduction of all change, in the physical world to movements of atoms produced independently of time by their central forces; or, in other words, natural science is the resolution of natural processes into the mechanics of atoms (Du Bois-Reymond, 1874, p. 17)– or of course the more recent genetic or molecular reductionism, crisply described by David Hull as follows: "both scientists and philosophers take ontological reduction for granted... Organisms are 'nothing but' atoms, and that is that" (Hull, 1981, p. 282).

Why is the Darwinian-inspired form of reductionism different from the above cases? Because they all amount to so many "ontological commitments" in Quine's sense (an ontological commitment means a commitment towards the existence of a particular set of objects: one thinker may believe in the existence of tables, chairs but also mathematical entities as real, while another might 'commit' to all three of these plus unicorns, so that their respective commitments correspond to a type of statement which is only true if objects of this type exist; Quine, 1961, p. 8, 12). The other forms of reductionism all are committed to a traditional distinction between the essential and the contingent, permanence and change ... whereas theories founded on chance are by definition, anti-essentialist.

Recall the comparison I sketched out above, between Kupiec's Darwinian invocation of chance contra essences, and Althusser's Lucretian invocation of the "random encounters" of molecules. One might object that the first is a scientific claim, in contrast to the second which is a philosophical usage of an ancient text – which itself seamlessly combined physics and metaphysics. But it seems that for Kupiec, as for Quine whom he does not mention, "ontology is part of the body of science itself and cannot be separated from it"

<sup>7</sup> John Tyndall (1820–1893) was an ideologist of Darwinism who in 1874 gave a very influential lecture at the British Association for the Advancement of Science in Belfast – thereafter known as the 'Belfast Address' (Tyndall, 1874) – arguing for science against religion, but also making specific points about evolutionary theory and its impact on our thinking, as a demystifying force against teleology and other ideas; very much what Dennett was to describe as a "universal acid" (Dennett, 1995, 63f.).

(Quine, 1961, p. 45, note 20, quoting Meyerson, 1908/1951). And in both cases, the Lucretian/Darwinian insistence on chance as explanatory has (philosophically) anti-essentialist consequences – what Dennett called a "universal acid" or a "universal solvent," in the sense of a method that dissolves many of our naïve preconceptions about the world, the objects that inhabit it as well our place in it (Dennett, 1995, 63f., p. 521). Of course, Dennett's way of putting it keeps us in the safe zone where science is a reliable provider of truths (or practical regularities) and common sense or 'folk psychology' is like a naughty child that occasionally has to be called back to order. In contrast, there is a different kind of radicalism implicit in the Lucretian project of "emptying the world of any substantiality, any necessity, any form that would be constitutive of its being – preventing any attempt to recreate a first philosophy" (Bourdin, 2005, p. 142). Granted, Kupiec's target is not Plato or Descartes or Hegel, but rather a specifically biological essentialism. But, aside from the general Quinean point about the continuum on which both ontology and science are located, we can also specifically note that in dealing with the form/matter pair, the problem of 'information' and the dangers of the 'spiritualisation of matter', metaphysics is never far off.

The ontophylogenetic theory (Kupiec, 2009), in which chance is primary, seems closer to reductionism than to holism, as described so far. But it certainly seeks to find a 'third way' between the two:

Ontophylogenesis allows us to escape from the fetters created by these two types of theory in which biological thought has been trapped throughout its history; and if it provides this new perspective, it is because it totally renounces specificity to make room for probability. It does not depend on any principle of order which may be inherent in matter or given a priori. The organism is produced in its context by a non-finalist process in which environmental constraints act on intrinsically probabilistic molecular and cellular mechanisms. (Kupiec, 2009, p. 203)

The concept of ontophylogenesis, as its name indicates, fuses ontogenesis (the production of the individual) and phylogenesis (the production of the species); for Kupiec, this means (i) that life relies on intrinsically stochastic processes, (ii) that natural selection takes place in the internal environment and (iii) that it is the causal agent for the formation of the organism. Leo Buss was perhaps the first to observe that "The Modern Synthesis has not generated a theory of ontogeny" (Buss, 1987, p. 25), and he too stated, in the preface to his book, that he could not understand why one cannot be a holist and a reductionist at the same time (Buss, 1987, p. vii, referring to John Tyler Bonner). However, Buss sees this as a kind of broadening of the Darwinian construct, different to Kupiec, whose radical, deflationary instincts steer him away from 'holistic Darwinism' and other odd constructs of the past twenty years of biological theory. Kupiec, despite his criticisms of genetic reductionism, is more 'reduction-friendly' than most of these thinkers seeking to expand the remit of Darwinism – be it through development, cultural evolution, niche selection or other means.

## 6.

One may ask at this point, what happens to the organism in this triangulation (where we seem to be moving in the direction of a kind of enhanced reductionism rather than holism)? At first, we get perhaps too strong a form of demystification (that is, reduction), with Kupiec's frequent accusations of 'animism' – that holism is animistic in the sense that it attributes an inherent creative force or activity to matter itself – which risk losing sight, not of the mysterious *norganism* or the organism as the bearer of an internal 'subjectivity' and 'temporality' which remove from it from the

physical world, but at the very least, of the functional integration of organisms.

Consider the case of teleology. Kupiec wheels out the old, reliable war machine of the Scientific Revolution with its heroic demystification of the world (as bearer of, e.g. occult qualities) and rejection of final causes, along with animism (Kupiec, 2009, p. 69). And it may be useful to dispel any residual concepts of a ‘finalistic’ teleology, which is often anthropomorphic, like that defended by the organismic biologist E.S. Russell:

The organism strives to persist in its own being, and to reach its normal completion or actualization. This striving is not as a rule a conscious one, nor is there often any foresight of the end, but it exists all the same, as the very core of the organism’s being (Russell, 1950, p. 108, citing his own earlier work *The Directedness of Organic Activities*).

But it is simple enough to defend a weaker form of teleology, in which – in a classic sort of example – the moth’s stripes or the polar bear’s colour can be teleologically described – in a *weak teleological sense* – as pointing to the camouflaging as leading to the (past) natural selection of their colour; not to a *strong teleological* claim that this camouflage predicts something about the future. And it seems dogmatic to reject the existence of a weaker sense of an inherent teleology in organisms, including their functional integration (Ruse, 1989, p. 1066). Surely Kupiec, as a Darwinian, could have allowed for at least as much as teleology in the biological world as Darwin did, not least given that if there is any teleology in Darwin’s world, “it is only because there is also a great deal of chance and accident in it” (Depew and Weber, 1996, p. 147). The argument against ‘animism’ is also too strong in the sense that it cannot do justice to the difference between organisational models (in the sense of Moreno et al.) as distinct from the more vitalistic, subjectivist models of organism like Varela’s, which, like Goldstein, privilege interiority over a ‘mere spatiality’ (patently obvious in Weber and Varela, 2002; Rudrauf et al., 2003), calling for “an expanded notion of the physical to account for the organism or living being” (Thompson, 2007, p. 238). Organisational models, like Kupiec’s own ontophylogenesis, are not in the business of foundationalist ontological commitments.

However, on the other hand we also get an interesting kind of residual vitalism (in the non-pejorative sense in which this term also applies to Claude Bernard, who after all is something of a father figure in the analysis of ontophylogenesis). For Bernard knew how to play a double game, both reductionist and vitalist, depending on the level of analysis (Kupiec, 2009, sections 6.1, 6.2; Coleman, 1985, on Bernard). Bernard could almost be a selfish-gene theorist when he says that “organs and systems do not exist for themselves, but for the cells, for the innumerable anatomical elements which comprise the organic edifice” (Bernard, 1879/1885, I, p. 358). The equivalent in Kupiec would be this anti-organistic statement: “there is no final aim in the organisation established of creating the organism for its own sake as an individual unit. It is the consequence of a process which ensures as best it can the life of cells” (Kupiec, 2009, p. 124). But Bernard also has more vitalistic moments:

[W]hat distinguishes a living machine is not the nature of its physico-chemical properties, complex as they may be, but rather the creation of the machine which develops under our eyes in conditions proper to itself and according to a definite idea which expresses the living being’s nature and the very essence of life (Bernard, 1865/1927, p. 93).

The more Darwinian emphasis in Kupiec, like in Lewontin (or Dennett or Dewey in their respective contexts) means that the

question of ‘what is an organism?’ (or a “living machine” in Bernard’s terms) is non-operative. Neither the questions posed by the theory nor the types of answer it seeks for, involve definitions of what an organism is; there is no particular insistence, e.g., on the idea that organisms are integrated entities rather than collections of discrete objects (Gould and Lewontin, 1979, p. 585). We are closer here to the processual character of Lewontin’s interactionism, as described above – where the organism is simply a place-holder for an intermediate location between various levels of a given system, including genes and environment. A more vitalist thinker would object here that by leaving ontology so far behind, we end up in a “night in which all cows are black” (Hegel, 1807/1979, p. 9), like functionalism in the philosophy of mind, in which, as memorably expressed by its great defender Hilary Putnam, “we could be made of Swiss cheese and it wouldn’t matter” (Putnam, 1975, p. 291; for some critical assessment of functionalism see Wolfe, 2006). That is, we end with a biophysics, a computational model, a mathematical model rather than with an embodied analysis.

## 7. Conclusion

The confrontation between chance, holism and reductionism – their triangulation, as I have called it, namely, the attempt to evaluate Kupiec’s new brand of Darwinism in terms of its way of positioning itself with respect to these ‘families’ of theoretical positions – produces a de-essentialised vision of Nature in general and the status of living beings in particular, without however entirely overcoming the need to address the latter status. Most interesting perhaps is what happens to the concept of determinism. For in the end, even if I initially noted the parallel between libertarianism, determinism and compatibilism on the one hand and their biological analogues (say, autopoiesis/organicism, genetic determinism and work such as Lewontin’s and Kupiec’s), what is really happening is a more subtle, more embodied reconstruction of certain components of determinism.

Determinism is less strictly opposed to stochasticity than one often hears. As Levins and Lewontin note, “the entire development of molecular biology shows the continuing power of simple deterministic models of the ‘bête-machine’ nor is there the slightest reason to introduce stochasticity into models of, say, how an increase in adrenalin secretion will affect the concentration of sugar in the blood” (Levins and Lewontin, 1980, p. 70); “thus stochastic processes may be the basis of deterministic process and deterministic the basis of stochastic. They do not exclude each other” (Levins and Lewontin, 1980, p. 72). But the sort of determinism at work in either Levins and Lewontin or Kupiec is a far cry from Dawkins’ claim that we are “gigantic lumbering robots” programmed by our genes (Dawkins, 1976, p. 21; useful discussion in Godfrey-Smith, 2001). Kupiec’s reappropriation of Darwinism away from the Modern Synthesis leads him to reject the ‘phenotype as expression of the genotype’ conception, in a way which injects Lucretian elements into the Darwinian framework. Similarly, the concept of reduction is still at work here, but not in such an ontologically strict sense; more as a heuristic (Gayon, 2009/2011). Like Buss, Kupiec clearly feels that “the theory of evolution has never proven a static construct” (Buss, 1987, p. 196).

Conversely, chance is not just an ‘empty word’, a word “devoid of meaning” as classic determinists would have it (e.g. D’Holbach, 1990, II.v, p. 158<sup>8</sup>); it has more creativity attached and, perhaps,

<sup>8</sup> D’Holbach (or Diderot, who is known to have contributed a good deal to the book) adds in a note to this passage, that “the molecules of matter may be compared to loaded dice, since they always produce certain pre-determined effects; as these molecules vary essentially, in themselves and in their combinations, they are loaded in infinitely various ways” (D’Holbach, 1990, p. 159, note 41).

a kind of ontological reality (for discussion see Merlin, 2009/2011). Kupiec often insists that ‘cellular Darwinism’ is meant to break away from the opposition between holism and reductionism, between top–down and bottom–up perspectives. But this applies also to the equally venerable opposition between chance and determinism, which in some cases is a false dichotomy (Wolfe, 2010c). For what looks like order at one level of organisation may look like disorder at another level; “notions such as those of ‘direction,’ ‘organisation’ or ‘randomness’ should be explicitly relativised to the unit in a hierarchy where they become relevant” (Falk and Sarkar, 1992, p. 470). Granted, from the standpoint of biology this privileging of chance need not entail either a holistic or a reductionist outlook, and conversely, emphasis on complex variation and selection models, taking Darwinism into, e.g. systems dynamics can be found elsewhere (Bickhard and Campbell, 2003); but I am speaking in conceptual terms – and as noted, sometimes Kupiec also seems to be making a contribution to natural philosophy, much as Monod or Mayr did before him, and, albeit differently, as Oyama also does today.<sup>9</sup> But to be clear, I am not claiming that what we learn here is a ‘new theory of chance’; rather, it is an anti-essentialist vision of organisms or living systems which navigates between various excesses (holism and reductionism), using an appeal to chance, stochasticity and generally Darwinian concepts as a background.

Lastly, what I’ve called the Lucretian elements in Kupiec’s Darwinism also explain its deliberate demystifying tone, challenging our anthropomorphic conceptions – of what a species is (following Darwin) or even an individual, over which there is after all so little consensus. This challenging aspect matches up with what Dennett called the “universal acid” aspect of evolutionary theory, which, oddly enough, Hans Jonas had also noted, a generation earlier – and in his conceptual world this became “existentialism”: “nineteenth-century evolutionism, which completed the Copernican revolution in ontology, is an apocryphal ancestor (along with the more official ones) of present-day existentialism” (Jonas, 1966, p. 47). Indeed, Dennett too acknowledges that evolutionary theory can have the effect of making most of our intuitions about life seem absurd (Dennett, 1995, p. 153). But whether we identify this type of thinking as Lucretian, Darwinian or existentialist, we should clearly see its challenge to hyper-rationalist or architectonic conceptions of order: the anti-essentialist dimension implies a rejection or at least a cautionary attitude, towards both the faith in the absolute, autonomous existence of higher-level systems (as found often in organicist theory) and the faith in the absolute explanatory power of componential analysis (as found always in reductionism).

Recall Kupiec’s point that both reductionism (specifically, genetic determinism) and holism posit “a first principle...which structures the world and directs processes,” a “principle of order” (Kupiec, 2009, p. 77). Contemplating Kupiec’s work today, I am reminded of Goethe’s rather pitiful confession of fear, faced with the Lucretian anarchy of Diderot’s world – he doubtless would have felt the same about Darwin; and today about Kupiec. Reacting to the materialist Diderot (who he also admired, and whose novel *Le Neveu de Rameau* he translated into German), Goethe, thinker of morphogenesis, *Urpflanze* and a hierarchy in Nature, wrote: “Astonishing and excellent Diderot, why always use your great intellectual powers to produce disorder rather than order?” (Goethe 1798/1998, 1996, p. 196). This disorder is that of the living world in its unpredictability – teratological, transformist, classically-Darwinian or cellular-Darwinian.

## Acknowledgements

I thank Thomas Pradeu for his critical remarks on an earlier draft, and I benefited greatly from the reviewers’ comments.

## References

- Althusser, L., 1994. In: Matheron, F. (Ed.), 1994. *Écrits philosophiques et politiques*, vol. 1. Stock/IMEC, Paris.
- Althusser, L., 2006. G.M. Goshgarian (Trans.). In: Matheron, F., Corpet, O. (Eds.), *Philosophy of the Encounter: Later Writings, 1978–1987*. Verso, London.
- Aristotle, 1984. *Physics*. In: Barnes, J. (Ed.), 1984. *The Complete Works of Aristotle*, vol. 1. Princeton University Press, Princeton.
- Ash, M.G., 1995. *Gestalt Psychology in German Culture*. Cambridge University Press, Cambridge.
- Bechtel, W., 2007. Biological mechanisms: organized to maintain autonomy. In: Boogerd, F., Bruggeman, F.J., Hofmeyr, J.-H.S., Westerhoff, H.V. (Eds.), *Systems Biology: Philosophical Foundations*. Elsevier, Amsterdam, pp. 269–302.
- Bernard, C., 1865/1927. *An Introduction to the Study of Experimental Medicine*. Henry Schuman, New York.
- Bernard, C., 1879/1885. *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux*, vol. 1. J.-B. Baillière, Paris.
- Bickhard, M.H., Campbell, D.T., 2003. Variations in variation and selection: the ubiquity of the variation-and-selective-retention ratchet in emergent organizational complexity. *Found. Sci.* 8, 215–282. doi:10.1023/A:1025046917589.
- Bickle, J., 2006. Reducing mind to molecular pathways: explicating the reductionism implicit in current cellular and molecular neuroscience. *Synthese* 151, 411–434. doi:10.1007/s11229-006-9015-2.
- Block, N., 1998. Holism: mental and semantic. In: Craig, E. (Ed.), *Routledge Encyclopedia of Philosophy*. Routledge, London, pp. 488–493.
- Bourdin, J.-C., 2005. La rencontre du matérialisme et de l’aléatoire chez Louis Althusser. *Multitudes* 21 (2), 139–147. doi:10.3917/mult.021.0139. <http://www.cairn.info/revue-multitudes-2005-2-page-139.htm>.
- Buss, L.W., 1987. *The Evolution of Individuality*. Princeton University Press, Princeton.
- Coleman, W., 1985. The cognitive basis of the discipline: Claude Bernard on physiology. *Isis* 76, 49–70. doi:10.1086/353737.
- Dawkins, R., 1976. *The Selfish Gene*. Oxford University Press, Oxford.
- de La Mettrie, J.O., 1748/1960. *L’Homme-Machine*. Vartanian, A. (Ed.), Princeton University Press, Princeton.
- Dennett, D.C., 1995. *Darwin’s Dangerous Idea*. Simon & Schuster, New York.
- Depew, D., Weber, B., 1996. *Darwinism Evolving: Systems Dynamics and the Genealogy of Natural Selection*. MIT Press, Cambridge, Mass.
- Dewey, J., 1910/2007. The influence of Darwin on philosophy. In: Hickman, L., Browning, D. (Eds.), *The Influence of Darwin on Philosophy and Other Essays*. Southern Illinois Press, Carbondale, IL, pp. 5–12.
- Du Bois-Reymond, E., 1874. The limits of our knowledge of nature (original publication 1872). *Popular Science Monthly* 5, 17–32.
- Ereshesfsky, M., 2010. What’s wrong with the new biological essentialism. *Phil. Sci.* 77 (5), 674–685. Stable URL: <http://www.jstor.org/stable/10.1086/656545>.
- Esfeld, M., 1999. Physicalism and ontological holism. *Metaphilosophy* 30 (4), 319–337. <http://dx.doi.org/10.1111/1467-9973.00141>.
- Falk, R., Sarkar, S., 1992. Harmony from discord. *Biol. Phil.* 7 (4), 463–472. doi:10.1007/BF00130064.
- Gayon, J., 2009/2011. Déterminisme génétique, déterminisme bernardien, déterminisme laplacien. In: Gandrillon, O., Kupiec, J.J., Morange, M. (Eds.), *Le hasard au cœur de la cellule*. Syllèpe, Paris, pp. 79–90, new edition, Editions Matériologiques, Paris, pp. 115–129.
- Gigandet, A., 2002. *Lucrèce vu en songe. Diderot, Le rêve de D’Alembert et le De rerum natura*. *Rev. Mét. Mor.* 35 (3), 415–427. doi:10.3917/rmm.023.0415.
- Godfrey-Smith, P., 2001. Three kinds of adaptationism. In: Orzack, S.H., Sober, E. (Eds.), *Adaptationism and Optimality*. Cambridge University Press, Cambridge, pp. 335–357.
- Goethe, J.W., 1798/1998. *Diderots Versuch über die Malerei*. In: Apel, F. (Ed.), *Goethe, Ästhetische Schriften, 1771–1805*. Deutscher Klassiker Verlag, Frankfurt, pp. 559–608 (*Sämtliche Werke*, Bd. 18).
- Goethe, J.W., 1996. *Écrits sur l’art*. J.-M. Schaeffer (Trans.). GF-Flammarion, Paris.
- Goldstein, K., 1995. *The Organism: A Holistic Approach to Biology Derived from Pathological Data in Man* (original publication 1934). American Book Company, New York.; reprint, Zone Books, New York.
- Gould, S., Lewontin, R., 1979. The Spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. *Proc. Roy. Soc. Lond. B Biol. Sci.* 205, 581–598. doi:10.1098/rspb.1979.0086.
- D’Holbach, B.P.-H.T., 1990. *Système de la Nature ou des lois du monde physique et du monde moral* (original publication 1770). In: Boulad-Ayoub, J. (Ed.), *Fayard-Corpus*, Paris.
- Hegel, G.W.F., 1807/1979. *Phenomenology of Spirit* (Trans.) A.V. Miller. Oxford University Press, Oxford.
- Hull, D., 1981. Philosophy and biology. In: Fløistad, G. (Ed.), 1981. *Contemporary Philosophy: a New Survey*, vol. 2. Martinus Nijhoff, The Hague, pp. 281–316.
- Huxley, J., 1971. *Memories*. Harper & Row, New York.
- Jonas, H., 1966. Is god a mathematician? The meaning of metabolism. In: Jonas, H. (Ed.), *The Phenomenon of Life. Towards a Philosophical Biology*. Harper & Row/Dell, New York, pp. 64–98.

<sup>9</sup> I thank both reviewers for remarks leading me to see this point.

- Kimura, M., 1983. *The Neutral Theory of Molecular Evolution*. Cambridge University Press, Cambridge.
- Kupiec, J.-J., 1996. A chance-selection model for cell differentiation. *Cell Death Differ.* 3, 385–390.
- Kupiec, J.-J., 1999. L'influence de la philosophie d'Aristote sur l'élaboration de la théorie de l'évolution et sur la génétique. *Rev. Eur. Sci. Soc.* 37 (115), 89–116. Stable URL: <http://www.jstor.org/stable/40370372>.
- Kupiec, J.-J., 2009. *The Origin of Individuals*. World Scientific, Singapore.
- Kupiec, J.-J., 2010. On the lack of specificity of proteins and its consequences for a theory of biological organization. *Prog. Bioph. Mol. Bio.* 102, 45–52. doi:10.1016/j.pbiomolbio.2009.11.002.
- Kupiec, J.-J., Sonigo, P., 2000. *Ni Dieu, ni gène*. Éditions du Seuil, Paris.
- Kupiec, J.-J., Gandrillon, O., Morange, M., Silberstein, M. (Eds.), 2009/2011. *Le hasard au cœur de la cellule. Probabilités, déterminisme, génétique*. Syllepse, Paris. new expanded edition, Editions Matériologiques, Paris.
- Laplane, L., 2011. Le mystère de la genèse des individus. *Critique* 764–765, 143–152.
- Levins, R., Lewontin, R.C., 1980. Dialectics and reductionism in ecology. *Synthese* 43 (1), 47–78. doi:10.1007/BF00413856.
- Lewontin, R.C., 1970. The units of selection. *Ann. Rev. Ecol. Syst.* 1, 1–18. doi:10.1146/annurev.es.01.110170.000245.
- Lewontin, R.C., 1983/1985. The Organism as the Subject and Object of Evolution. In: Levins, R., Lewontin, R.C. (Eds.), *The Dialectical Biologist*. Harvard University Press, Cambridge, Mass., pp. 85–106.
- Loeb, J., 1912. *The Mechanistic Conception of Life: Biological Essays*. University of Chicago Press, Chicago.
- Merlin, F., 2009/2011. Pour une interprétation objective des probabilités dans les modèles stochastiques de l'expression génétique. In: Gandrillon, O., Kupiec, J.-J., Morange, M. (Eds.), *Le hasard au cœur de la cellule*. Syllepse, Paris, pp. 79–90, new edition, Editions Matériologiques, Paris, pp. 215–252.
- Meyerson, E., 1908/1951. *Identité et réalité*. Vrin, Paris.
- Monod, J., 1970. *Le Hasard et la nécessité. Essai sur la philosophie naturelle de la biologie moderne*. Éditions du Seuil, Paris.
- Monod, J., 1971. *Chance and Necessity: an Essay on the Natural Philosophy of Modern Biology*. Alfred A. Knopf, New York.
- Oyama, S., 1985/2000. *The Ontogeny of Information: Developmental Systems and Evolution*, 2nd revised ed. Duke University Press, Durham, NC.
- Oyama, S., 2000. *Evolution's Eye: a Systems View of the Biology-Culture Divide*. Duke University Press, Durham, NC.
- Oyama, S., 2009. Compromising positions: the minding of matter. In: Barberousse, A., Pradeu, T., et al. (Eds.), *Mapping the Future of Biology. Evolving Concepts and Theories*. Springer, Dordrecht, pp. 27–45.
- Oyama, S., 2010. Biologists behaving badly: vitalism and the language of language. *Hist. Phil. Life Sci.* 32 (2–3), 401–423.
- Pépin, F., 2012. Claude Bernard et Laplace: d'un déterminisme physique vers un déterminisme proprement biologique ? In: Charbonnat, P., Pépin, F. (Eds.), *Matière première 2: Le déterminisme entre sciences et philosophie*. Éditions Matériologiques [materiologiques.com], Paris, pp. 41–79.
- Pépin, F., 2012. The randomness of life. A philosophical approach inspired from the enlightenment. *Prog. Bioph. Mol. Bio.* 110, 121–128.
- Peterson, E.L., 2010. *Holism and evolution in biology and Anthropology: the challenge of Gregory Bateson and C. H. Waddington to biological Orthodoxy, 1924–1980*. PhD Dissertation, University of Notre Dame, Program in history and philosophy of science.
- Putnam, H., 1975. *Philosophy and our mental life*. In: Putnam, Mind, Language, and Reality. Philosophical Papers, vol. 2. Cambridge University Press, Cambridge, pp. 291–303.
- Quine, W.V.O., 1961. *From a Logical Point of View*, second ed., Harvard University Press, Cambridge, Mass.
- Rudrauf, D., Lutz, A., Cosmelli, D., Lachaux, J.-P., Le Van Quyen, M., 2003. From autopoiesis to neurophenomenology: Francisco Varela's exploration of the biophysics of being. *Biol. Res.* 36 (1), 27–65.
- Ruiz-Mirazo, K., Moreno, A., 2004. Basic autonomy as a fundamental step in the synthesis of life. *Artif. Life* 10, 235–259. doi:10.1162/1064546041255584.
- Ruiz-Mirazo, K., Etxeberria, A., Moreno, A., Ibáñez, J., 2000. Organisms and their place in biology. *Theor. Biosci.* 119, 209–233. doi:10.1007/s12064-000-0017-1.
- Ruse, M., 1989. Do organisms exist? *Amer. Zool.* 29, 1061–1066. doi:10.1093/icb/29.3.1061.
- Russell, E.S., 1950. The 'Drive' element in life. *Brit. Jour. Phil. Sci.* 1 (2), 108–116. Stable URL: <http://www.jstor.org/stable/685806>.
- Schaeffer, J.-M., 2007. *La fin de l'exception humaine*. Gallimard-NRF, Paris.
- Schrödinger, E., 1944. *What Is Life? The Physical Aspect of the Living Cell*. Cambridge University Press, Cambridge.
- Shapiro, L., 2007. The embodied cognition research programme. *Philos. Compass* 2 (2), 338–346. doi:10.1111/j.1747-9991.2007.00064.
- Smuts, J.C., 1926/1999. *Holism and Evolution*. Sierra Sunrise Books, Sherman Oaks, CA.
- Thompson, E., 2007. *Mind in Life: Biology, Phenomenology, and the Sciences of Mind*. Harvard University Press, Cambridge, Mass.
- Tyndall, J., 1874. *Address Delivered Before the British Association Assembled at Belfast, with Additions*. Longmans, Green, and Co., London. Online at URL: [http://www.victorianweb.org/science/science\\_texts/belfast.html](http://www.victorianweb.org/science/science_texts/belfast.html).
- Weber, A., Varela, F.J., 2002. Life after Kant: natural purposes and the autopoietic foundations of biological individuality. *Phen. Cog. Sci.* 1, 97–125. doi:10.1023/A:1020368120174.
- Werner, E., 2009. Evolutionary embryos. *Nature* 460 (2), 35–36. doi:10.1038/460035a.
- Wolfe, C.T., 2006. Un matérialisme désincarné: la théorie de l'identité cerveau-esprit. *Matière Première* 1, 77–100.
- Wolfe, C.T., 2010a. Endowed molecules and emergent organization: the Maupertuis-Diderot debate. *Early Sci. Med.* 15, 38–65. <http://dx.doi.org/10.1163/138374210X12589831573063>.
- Wolfe, C.T., 2010b. Do organisms have an ontological status? *Hist. Phil. Life Sci.* 32 (2–3), 195–232.
- Wolfe, C.T., 2010c. Un colpo di dadi non cancellerà mai il caso: il determinismo lucreziano dopo Locke. In: Mormino, G., Morfino, V., del Lucchese, F. (Eds.), *Lucrezio e la modernità*. Bibliopolis, Naples, pp. 235–251.
- Wolfe, C.T., 2011. Vitalism. In: Gargaud, M., et al. (Eds.), *Encyclopedia of Astrobiology*. Springer, Berlin, pp. 1749–1750.



# Systems biology: current status and challenges

Anze Zupanic<sup>1</sup> · Hans C. Bernstein<sup>2,3</sup> · Ines Heiland<sup>4</sup>

Received: 2 December 2019 / Revised: 2 December 2019 / Accepted: 2 December 2019 / Published online: 13 January 2020  
© Springer Nature Switzerland AG 2020

## Abstract

We put together a special issue on current approaches in systems biology with a focus on mathematical modeling of metabolic networks. Mathematical models have increasingly been used to unravel molecular mechanisms of complex dynamic biological processes. We here provide a short introduction into the topics covered in this special issue, highlighting current developments and challenges.

**Keywords** Systems biology · Mathematical modeling · Metabolic pathway analysis · Network dynamics · Multi-scale modeling

Systems biology has a wide range of definitions and covers an even wider range of different approaches and topics. We here refer to systems biology as an area of research that uses mathematical modelling in tight interconnection with experimental approaches to understand the mechanisms of complex biological systems and predict their behaviour across scales—molecular-to-organismal. This special issue focuses on metabolic modelling within this context where topics range from single-cell systems to multi-tissue and whole-body models. There are generally two different approaches to metabolic modelling. One is the dynamical modelling of detailed targeted pathways using kinetic rate laws, which allows us to describe steady-state fluxes and the dynamics of metabolite concentrations. As kinetic rates are often measured only for a limited number of reactions, these models usually cover only a small part of cellular metabolism. These approaches are also often used to describe signal

transduction pathways. Interestingly, most dynamic models to date have been built for higher eukaryotes, mainly mammals. In contrast, whole cell or genome-wide metabolic models are still mainly used to analyze microbial systems. Genome-scale modelling approaches describe the whole-cell metabolic networks using methods known as ‘constraint-based metabolic modelling’. The latter are largely based on the assumption of evolutionary optimality of cellular metabolism. The disadvantage of these models is that the concentration of modelled internal metabolites—those that do not represent sources or sinks to the system—cannot be considered independently from each other. In addition, simulations of this type strongly depend on the particular assumptions made about optimization and corresponding optimization functions used to constrain the solution space. To overcome these limitations, more research groups have engaged ‘hybrid modelling approaches’, either scaling up of dynamic models or simplifying genome-scale models. Targeting the latter, the review provided by Singh and Lercher [1] discusses model reduction strategies that shall enable detailed dynamic description of genome-scale metabolism through model reduction.

Notwithstanding drawbacks, both dynamic- and genome-scale metabolic modelling approaches have been very successful in both biotechnology and for the prediction of metabolic alteration in disease. A number of different approaches and model systems, ranging from bacteria to human, are presented in this special issue:

De Groot et al. [2] analyze general metabolic features of model organisms, such as *Escherichia coli* and

---

✉ Ines Heiland  
ines.heiland@uit.no

<sup>1</sup> Department of Biotechnology and Systems Biology, National Institute of Biology, Vecna Pot 111, 1000 Ljubljana, Slovenia

<sup>2</sup> Faculty of Biosciences, Fisheries and Economics, UiT, The Arctic University of Norway, Tromsø, Norway

<sup>3</sup> The Arctic Centre for Sustainable Energy, UiT, The Arctic University of Norway, Tromsø, Norway

<sup>4</sup> Department of Arctic and Marine Biology, UiT The Arctic University of Norway, Biologibyget, Framstedet 39, 9037 Tromsø, Norway

*Saccharomyces cerevisiae*. By comparing several models available to date, they identify modelling constraints that lead to the robust prediction of the often-discussed counterintuitive effect of overflow metabolism. In contrast, Park et al. [3] discuss why pathogenetic bacteria such as pseudomonads in isolation or bacterial communities often behave differently than the model organisms and show that their (evolutionary) success may be achieved through the adaptation of alternative metabolic strategies with respect to nutrient usage. The reviews by Ewald et al. [4] and Pecht et al. [5] build upon multicellular and multi-species systems by reviewing current modelling approaches to study host–pathogen interactions.

In recent years, there has been a concerted effort to improve our understanding of the metabolism of multicellular eukaryotes, such as humans or plants. Although examples of genome-scale modelling exist for these systems, their predictive capacity still remains behind those for single-cell organisms. Thus, dynamic metabolic modelling approaches describing specific pathways of interest are very common. As an example, Mazat et al. [6] provide a review of modelling approaches and current knowledge of ROS production in mitochondria. While there are fewer plant studies compared to human and mammalian ones, an increasing number of systems biology studies are looking into resistance of plants to environmental stress and accompanying metabolic/nutritional changes. In this respect, Holzheu and Kummer [7] review current modelling approaches used to study the model plant *Arabidopsis thaliana* and provide examples on how they have increased our understanding of plant metabolism and their potential for agricultural and medical practice.

Most models to date only target one level of organization, and real multiscale approaches are still limited. One reason is that the level of detail needs to be adjusted when going from single cell, over multicellular systems and tissues to the whole-body level, which requires to make assumptions that in turn may limit the predictive capacity and the possibilities for emerging behaviour. As part of this special issue, Shaw and Cheung [8] discuss the advantages and disadvantages of multi-tissue whole-plant modelling approaches in comparison with single-tissue approaches.

Challenges for multiscale modelling approaches do not only arise from limitations in our ability to mathematically represent a biological system. The challenges are inherent to the complex biology observed in many of our study systems and from limitations imposed from experimental observation. Different techniques need to be used to study different levels of organization. Sometimes, experimental data are only available from in vitro studies, while in vivo measurement can be very different or impossible. This topic is discussed in the review provided by Clarelli et al. [9], which emphasizes these limitations in the context of predicting in vivo antibiotic responses.

The reviews provided in this special issue cover different methods and examples, in which systems biology was used to further our understanding of biology. Many more have been developed in recent years, covering all levels of organization, time scales as well as using different mathematical approaches, ranging from cellular automata to logical networks. As the field has expanded and more researchers have started using systems biology approaches in their work, the number of meetings covering systems biology has also increased. For example, the conferences of the International Study Group for Systems Biology (ISGSB—[igsb.org](http://igsb.org)), which also served as the seed for this special issue, are held on a biannual basis, whereas the larger International Conference in Systems Biology (ICSB) is held every year. The next ISGSB conference will be held in Stellenbosch, South Africa, from the 14–19 September 2020, whereas the next ICSB will be held in Connecticut from 10–16 October 2020 (<http://icsb2020.bioscience-ct.net/>).

## References

1. Singh D, Lercher MJ (2019) Network reduction methods for genome-scale metabolic models. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03383-z>
2. de Groot DH, Lischke J, Muolo R, Planque R, Bruggeman FJ, Teusink B (2019) The common message of constraint-based optimization approaches: overflow metabolism is caused by two growth-limiting constraints. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03380-2>
3. Park H, McGill SL, Arnold AD, Carlson RP (2019) Pseudomonad reverse carbon catabolite repression, interspecies metabolite exchange, and consortial division of labor. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03377-x>
4. Ewald J, Sieber P, Garde R, Lang SN, Schuster S, Ibrahim B (2019) Trends in mathematical modeling of host-pathogen interactions. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03382-0>
5. Pecht T, Aschenbrenner AC, Ulas T, Succurro A (2019) Modeling population heterogeneity from microbial communities to immune response in cells. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03378-w>
6. Mazat JP, Devin A, Ransac S (2019) Modelling mitochondrial ROS production by the respiratory chain. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03381-1>
7. Holzheu P, Kummer U (2019) Computational systems biology of cellular processes in *Arabidopsis thaliana*: an overview. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03379-9>
8. Shaw R, Cheung CYM (2019) Multi-tissue to whole plant metabolic modelling. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03384-y>
9. Clarelli F, Liang J, Martinecz A, Heiland I, Abel Zur Wiesch P (2019) Multi-scale modeling of drug binding kinetics to predict drug efficacy. *Cell Mol Life Sci.* <https://doi.org/10.1007/s00018-019-03376-y>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



World Class. Face to Face.

**COURSE ANNOUNCEMENT**

**SPRING 2021**

**Biol 476/576  
Epigenetics and Systems Biology**

**3 Credits  
Lectures – Recorded Online  
Discussions on Zoom, Thurs. 10:35-11:50 A.M.**

**Course Director: Dr. Michael Skinner**

**Line Number:  
SLN (476) – 08429  
SLN (576) – 08430**

Vancouver SLNs (476) – 15326 / (576) – 15327  
Tri-Cities SLNs (476) – 01740 / (576) – 01741

Lectures offered through Blackboard / Panopto and  
Discussion Sessions on WSU Zoom for all campuses

**Course Contents:**  
State of the art advances in epigenetics and its role in systems biology presented  
with applications in developmental biology, environmental epigenetics/toxicology,  
disease etiology, ecology and evolutionary biology.

**First Lecture, January 19, 2021**

Online Global Campus version of course offered to Global Campus Students  
(476) 10115 / (576) 10116

**“Epigenetics and Systems Biology”**

**Spring 2021 (Odd Years) – Course Syllabus  
Biol 476/576 Undergraduate/Graduate Course (3 Credit)  
SLN: (476) – 08429, (576) – 08430**

**Vancouver SLNs (476) – 15326 / (576) – 15327; Tri-Cities SLNs (476) – 01740 / (576) – 01741  
Time – Course Lectures Online on Blackboard/Panopto and Discussion Sessions on WSU Zoom  
Thursday 10:35 am – 11:50 am for all campuses**

**Lectures – Blackboard/Panopto Video Captured and Discussion Section Zoom session**

**Course Director - Michael Skinner, Abelson Hall 507, 335-1524, [skinner@wsu.edu](mailto:skinner@wsu.edu)**

**Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, [nilsson@wsu.edu](mailto:nilsson@wsu.edu)**

**Learning Objective -** The objective of the course is to learn the concept and critical role of systems to understand  
molecular, cell, development, physiology and evolutionary aspects of biology with a focus on the role of epigenetics  
in systems biology.

**Schedule/Lecture Outline –**

Week 1	(Lesson 1)	Systems Biology (History/ Definitions/ Theory)
Week 2	(Lesson 2)	Systems Biology (Networks & Emergence)
Week 3	(Lesson 3)	Systems Biology (Components: DNA to Phenotype)
Week 4	(Lesson 4)	Systems Biology (Genomics / Technology)
Week 5	(Lesson 5)	Epigenetics (History / Molecular Processes)
Week 6	(Lesson 6)	Epigenetics (Molecular Processes & Integration)
Week 7	(Lesson 7)	Epigenetics (Genomics and Technology)
Week 8	(Lesson 8)	Cell & Developmental Biology
Week 9	(Lesson 9)	Epigenetics of Cell & Developmental Biology
Week 10	(Lesson 10)	Environmental Impact on Biology
Week 11	(Lesson 11)	Environmental Epigenetics
Week 12	(Lesson 12)	Disease Etiology
Week 13	(Lesson 13)	Epigenetics & Disease Etiology
Week 14	(Lesson 14)	Evolutionary Biology & Genetics
Week 15	(Lesson 15)	Epigenetics & Evolutionary Biology
Week 16	(Lesson 16)	Grant Review/ Study Section Meeting

**Instruction Format -**

- One 1.5 hour overview/lecture per week (access on Panopto from class website)
- One 1.5 hour literature review/discussion session per week (Zoom session Thursdays 10:30- Noon)
- Start Zoom session January 19, 2021, Holidays: 2/25/21, 3/17/21 and 4/13/21

**Course Requirements -**

1. Attendance
2. Participation in literature and discussion sessions

Graduate Students:

3. Grant Proposal (12 page limit) due week 15
4. Student Grant Review session week 16

Undergraduate Students:

3. Two take home exams

**Grading and Evaluation-**

- Both in class attendance (10%) and discussion participation (25%) and (graduate students) the proposal (65%) or (undergraduate students) exams (65%) will be factors considered.
- Grading scale A(90%), B(80%), C(70%), D(60%), F(<60%)

**References and Textbook-**

- Reading literature and references provided one week prior to session
- No required textbook (suggested additional reading provided in handouts, but not required).

**Graduate Students**

**Grant Proposal**

**Outline:**

- Title
- Abstract
- Specific Aims / Hypothesis
- Background
- Preliminary Results
- Experimental Design and Methods
- References

(12 pp. single spaced typed limit, not including references)

**Key Points:**

- Specific aims should be focused and concise and clarify hypothesis
- Be as concise and direct as possible
- Work significance of proposal into grant when appropriate
- Use only critical preliminary results

**Additional Information:**

- Propose short-range studies to address long-range goals
- Write grant for 3 to 4 year period to complete studies
- Feasibility of success is critical, ask right type of question
- Experimental design needs to address hypothesis

**Score/Rating:**

Factors involved: Type question addressed, organization of thoughts, preliminary results, feasibility, reasonable completion expectations, focus of aims and proposed studies.

Score	Outstanding	Funded
1.0 - 1.5	Excellent	Probably Funded
1.5 - 2.0	Good	Accepted, but not Funded
2.0 - 2.5		
2.5 - 3.0	Satisfactory	
3.0 - 3.5	Adequate	
3.5 - 4.0	Fair	
4.0 - 5.0	Acceptable	

**Review:**

NIH Study Section style review with all students/fellows participating in the review. Primary and secondary reviewers will be selected and all grants will be critiqued.

**Note:**

Welcome to use opportunity to prepare grants for student orals or fellowship applications.

www.skinner.wsu.edu

WASHINGTON STATE UNIVERSITY

SKINNER LABORATORY

**Biol 476/576 "Epigenetics and Systems Biology" – Spring 2021**  
**COURSE ANNOUNCEMENT**  
**SYLLABUS**

**PANOPTO RESOURCES:**  
 Panopto: Getting Started  
 Panopto: Activating through Blackboard Learn  
 Blackboard Learn (Log-in page)  
 Discussion Session with Zoom

**Weeks 1 & 2**  
**WEEK 1 SYSTEMS BIOLOGY (HISTORY/ DEFINITIONS/ THEORY)**  
 January 19, 21 & 26 – Lecture Handout  
 January 19 – Panopto Lecture (log-in required)  
 January 21 – Panopto Lecture (log-in required)

**WEEK 2 SYSTEMS BIOLOGY (NETWORKS & EMERGENCE)**  
 January 26 – Panopto Lecture (log-in required)

**PANOPTO** GUIDE FOR STUDENTS

**1) Downloading Recorder**

- Log in to [wsu.hosted.panopto.com](http://wsu.hosted.panopto.com)
- Download link is in the upper right-hand corner

**2) Getting Help**

- Call Panopto at 1 (855.726.6786) between 5 a.m. 5 p.m. M-F
- Email [support@panopto.com](mailto:support@panopto.com)
- Visit <http://support.panopto.com/documentation>
- Visit CougTech in CUE 302

**3) Recording Spaces**

- Reserve a study space at [calendars.libraries.wsu.edu](http://calendars.libraries.wsu.edu)
- AMS in Holland 150. Phone: (509) 335-4535
- CougTech in CUE 302 also has a limited amount of spaces

**4) Laptop Checkout**

- AMS has a small number of laptops available for checkout
  - o Up to 90-minute checkouts
- The WSU Libraries also have laptops available
  - o Must stay within library buildings
- CougTech rents laptops to students, rates below:
  - o <https://cougtech.wsu.edu/Services/RentalRates.aspx>

**Spring 2021- Epigenetics and Systems Biology**  
**Lecture Outline – Systems Biology**  
 Michael K. Skinner – Biol 476/576  
 10:35-11:50 am, Tuesdays & Thursdays  
 January, 2021  
 Weeks 1 and 2

**Systems Biology**

- History and Definitions
- Reductionism/ Genetic Determination
- Holism/ Emergentism/ Homeostasis or Robustness
- Revolutionary and Evolutionary Systems Biology
- Networks and Computational Biology
- Basic Molecular and Cellular Components

**Required Reading**

Knepper et al. (2014) Systems biology versus reductionism in cell physiology. Am J Physiol Cell Physiol 307:C308-C309.

Wolfe CT. Chance between holism and reductionism: tensions in the conceptualisation of Life. Prog Biophys Mol Biol. 2012 Sep;110(1):113-20.

Zupanic A, Bernstein HC, Heiland I. Systems biology: current status and challenges. Cell Mol Life Sci. 2020 Feb;77(3):379-380.

**Background Book References**

**James A. Marcum (2009) The Conceptual Foundations of Systems Biology, Nova Science Publishers, Inc.**

Eberhard Voit (2012) A First Course in Systems Biology, Garland Science

Capra and Luisi (2014) The Systems View of Life, Cambridge University Press.

Leonie Ringrose (2017) Epigenetics and Systems Biology, Academic Press

**Spring 2021 – Epigenetics and Systems Biology**  
**Discussion Outline (Systems Biology)**  
 Michael K. Skinner – Biol 476/576  
 Weeks 1 and 2 (January 28, 2021)

**Systems Biology**

Primary Papers

1. Kitano H. (2002) Nature 420:206-210. (PMID: PMID: 12432404)
2. Morelli, et al. (2012) Science 336:187-191. (PMID: 22499940)
3. Goroehowski, et al. (2020) Front. Bioengineering & Biotechnology, 8:705 (PMID: 32671054)

**Discussion**

Student 1 - Ref #1 above  
 -What are simulation and in silico experiments?  
 -What are scale free networks?  
 -How can this computational approach help medicine?

Student 2 - Ref #2 above  
 -What are patterning strategies?  
 -What is mechanical deformation?  
 -How are gene networks involved?

Student 3 - Ref #3 above  
 -What is emergence?  
 -How can synthetic biology be used?  
 -What are the insights provided in systems biology?

## Systems Biology

Definition

History

Theory

Paradigm Shift

Parameters

Systems biology is a comprehensive quantitative analysis of the manner in which all the components of a biological system interact functionally over time. Such an analysis is executed by an interdisciplinary team of investigators that is also capable of developing required technologies and computational tools. In this model, biology dictates what new technology and computational tools should be developed, and, once developed, these tools open new frontiers in biology for exploration. Thus, biology drives technology and computation, and, in turn, technology and computation revolutionize biology.

*“systems biology is the study of an organism, viewed as an integrated and interacting network of genes, proteins and biochemical reactions which give rise to life” (Hood 2005).*

## Systems Biology Theory

Evolutionary Systems Biology- Extension of classical biology paradigm with new technology

Revolutionary Systems Biology- New paradigm shift in biology with altered perspective on causal relationships and systems

## Evolutionary Systems Biology History

Systems biology extension current paradigm and history of biology with new technology

300BC Aristotle, System has 4 properties or causes: Material, Formal, Efficient, Teleological

200AD Galen (Roman Physician), Teleological important role in organism function

1500s Fernel, Systematic approach Anatomy

1600s Harvey, Physiology, Cell Biology, Circulation

1700s Newton, Physics leads to mechanistic determinism to explain systems

La Mettrie, Define Biological Machine (eg Clock)

1800s Bernard, Father physiology and integration biological systems (milieu interieur)

1900s Cannon, Biological equilibrium and homeostasis

-Discovery DNA/Structure/Genes (Molecular Biology)

-Computational Biology (non-equilibrium thermodynamics and kinetics metabolism)

2000s -Genome Sequence

-Omics Technology

Ecosystem



Populations



Organisms



Organ systems



Organs



Tissues



Cells



Organelles



Macromolecules

Figure 1. Hierarchical relationships involved in reductionism. The figure is not complete or exhaustive since non-represented phenomena exist at both ends; rather, it is simply illustrative of hierarchical, causal relationships.

## Evolutionary System Biology Definitions

Extension of traditional biological paradigm

Marc Kirchner 2005

“Systems biology is the study of the behavior of complex biological organization and processes in terms of the molecular constituents”

Westerhoff and Alberghina 2005

Systems biology is “nothing but good old physiology” or that is “molecular biology claiming additional money”

Sorger 2005

“System biology aim is to build numerical models of biological processes and test the models experimentally”

## Scientific Paradigm Shift

(a) Normal science → Anomaly

(b) Anomaly → Crisis

(c) Crisis → Extraordinary science

(d) Extraordinary science → New normal science

Figure 7. Steps involved in a Kuhnian scientific revolution.

### Revolutionary Systems Biology History

- Jan Smuts (1870-1950), South Africa, Defined-**Holism** (Tendency in nature to form wholes that are greater than the sum of the parts through creative evolution)
- Alfred Whitehead (1861-1947), USA, Defined- **Organisms** (Philosophy of organism to explain the complexity of natural processes- including biological organisms)
- Ludwig von Bertalanffy (1901-1972), Austria, Defined- **Disequilibrium** (Biological organisms are open systems, which respond to changes in environment, such that disequilibrium is state of living organism and equilibrium is death)
- Norbert Wiener (1894-1964), USA, Defined- **Cybernetics** (Application mathematics to explain biological mechanisms)
- Joseph Woodger (1894-1981), UK, Defined- **Bauplan** (Bauplan as the essential structural plan or morphology of an organism body plan, eg vertebrates)
- Conrad Waddington (1905-1975), Scotland, Defined- **Epigenetics** (Discuss later)
- Walter Elsasser (1904-1991), Hungarian, Defined- **Biotonic** (Laws not reducible to physical or chemical laws)
  
- 1980s Theoretical Biology Holism (Elsasser and Laszlo) (Butterfly Effect)  
Chaos Theory (Mathematical approach complex systems)
- 1990s High throughput sequencing and expansion epigenetic area
- 2000s Sequence genome and transcriptome (Omics technologies)

Ecosystems



Populations



Organisms



Organ systems



Organs



Tissues



Cells



Organelles



Macromolecule

Figure 3. Hierarchical relationships involved in holism. The figure again is not complete or exhaustive but rather illustrative of hierarchical, causal relationships.

### Revolutionary Definitions for Systems Biology

- Leroy Hood (2005)  
"The inter-relationships of all the elements in a system rather than studying them one at a time"
- Methodological Approach-
  - 1) Develop simple descriptive, graphical, or mathematical model of how system functions
  - 2) Identify and define the various components of the system and their state (eg omics)
  - 3) Disturb the system with external perturbation and document changes in the components
  - 4) Integration of the two data sets from step 3 and comparison to model in step 1
  - 5) Adjust model until harmony or conjunction exists between data and model
- Hiroaki Kitano (2002)  
Four factors for comprehensive systems biology definition
  - 1) System Structure, organization of components (macromolecules, genes, cells, tissues etc)
  - 2) System Dynamics, interactions between or relationships of the various hierarchical levels over time
  - 3) Systems Control Method, regulatory mechanisms involved in the maintenance of the organizational hierarchy
  - 4) Systems Design Method, hierarchical organization with specific properties and manipulate

**Table 1. Comparison of features for revolutionary and evolutionary systems biology**

Revolutionary systems biology	Evolutionary systems biology
1. Holism	Reductionism
2. Top-down causation	Bottom-up causation
3. Epigenetics	Genetic determinism
4. Emergentism	Mechanism
5. Synergism	Synthesis
6. Robustness	Homeostasis
7. Nonlinear dynamics	Linear stasis

## Reductionism

The view that the ultimate scientific understanding of a range of phenomena is to be gained exclusively from looking at the constituents of these phenomena and their properties

### Ontological Reductionism

That complex phenomena are reducible to or determinable by simpler entities and forces that compose them (eg genetic determinism) and (bottom-up or upward causation)

### Methodological Reductionism

Reducing wholes to parts and explaining the higher levels in terms of lower ones as the ultimate direction for all scientific research (eg physics)

### Epistemological Reductionism

Reduction of scientific knowledge, whether in terms of theories, laws, or explanations, from a higher level of organization to that of a lower or more basic one

## The fall and rise of pharmacology--(re-)defining the discipline? Winquist RJ, Mullane K, Williams M.

Biochem Pharmacol. 2014 Jan 1;87(1):4-24.

### Abstract

Pharmacology is an integrative discipline that originated from activities, now nearly 7000 years old, to identify therapeutics from natural product sources. Research in the 19th Century that focused on the Law of Mass Action (LMA) demonstrated that compound effects were dose-/concentration-dependent eventually leading to the receptor concept, now a century old, that remains the key to understanding disease causality and drug action. As pharmacology evolved in the 20th Century through successive biochemical, molecular and genomic eras, the precision in understanding receptor function at the molecular level increased and while providing important insights, led to an overtly reductionistic emphasis. This resulted in the generation of data lacking physiological context that ignored the LMA and was not integrated at the tissue/whole organism level. **As reductionism became a primary focus in biomedical research, it led to the fall of pharmacology** However, concerns regarding the disconnect between basic research efforts and the approval of new drugs to treat 21st Century disease tsunamis, e.g., neurodegeneration, metabolic syndrome, etc. has led to the reemergence of pharmacology, its rise, often in the semantic guise of systems biology. Against a background of limited training in pharmacology, this has resulted in issues in experimental replication with a bioinformatics emphasis that often has a limited relationship to reality. The integration of newer technologies within a pharmacological context where research is driven by testable hypotheses rather than technology, together with renewed efforts in teaching pharmacology, is anticipated to improve the focus and relevance of biomedical research and lead to novel therapeutics that will contain health care costs.

## Neuropharmacology beyond reductionism - A likely prospect.

Margineanu DG.

Biosystems. 2016 Mar;141:1-9.

### Abstract

Neuropharmacology had several major past successes, but the last few decades did not witness any leap forward in the drug treatment of brain disorders. Moreover, current drugs used in neurology and psychiatry alleviate the symptoms, while hardly curing any cause of disease, basically because the etiology of most neuro-psychic syndromes is but poorly known. This review argues that this largely derives from the unbalanced prevalence in neuroscience of the analytic reductionist approach, focused on the cellular and molecular level, while the understanding of integrated brain activities remains flimsier. The decline of drug discovery output in the last decades, quite obvious in neuropharmacology, coincided with the advent of the single target-focused search of potent ligands selective for a well-defined protein, deemed critical in a given pathology. However, all the widespread neuro-psychic troubles are multi-mechanistic and polygenic, their complex etiology making unsuited the single-target drug discovery. An evolving approach, based on systems biology considers that a disease expresses a disturbance of the network of interactions underlying organismic functions, rather than alteration of single molecular components. Accordingly, systems pharmacology seeks to restore a disturbed network via multi-targeted drugs. This review notices that neuropharmacology in fact relies on drugs which are multi-target, this feature having occurred just because those drugs were selected by phenotypic screening in vivo, or emerged from serendipitous clinical observations. The novel systems pharmacology aims, however, to devise ab initio multi-target drugs that will appropriately act on multiple molecular entities. Though this is a task much more complex than the single-target strategy, major informatics resources and computational tools for the systemic approach of drug discovery are already set forth and their rapid progress forecasts promising outcomes for neuropharmacology.

## Overcoming the Newtonian paradigm: the unfinished project of theoretical biology from a Schellingian perspective.

Gare A.

Prog Biophys Mol Biol. 2013 Sep;113(1):5-24

### Abstract

Defending Robert Rosen's claim that in every confrontation between physics and biology it is physics that has always had to give ground, it is shown that many of the most important advances in mathematics and physics over the last two centuries have followed from Schelling's demand for a new physics that could make the emergence of life intelligible. Consequently, **while reductionism prevails in biology, many biophysicists are resolutely anti-reductionist**. This history is used to identify and defend a fragmented but progressive tradition of anti-reductionist biomathematics. It is shown that the mathematico-physico-chemical morphology research program, the biosemiotics movement, and the relational biology of Rosen, although they have developed independently of each other, are built on and advance this anti-reductionist tradition of thought. It is suggested that understanding this history and its relationship to the broader history of post-Newtonian science could provide guidance for and justify both the integration of these strands and radically new work in post-reductionist biomathematics.

## Holism (Revolutionary Systems Biology)

The living world consists in a reality that can be understood only in its global and inseparable unity. The whole is fundamental, not any one level. The whole is greater than the sum of its parts or of its levels.

### Ontological Holism

Putting together the parts will not produce the wholes (such as living systems) or account for their properties and behaviors. Downward causation claims that higher order entities determine causally the properties or behavior of lower-level entities.

### Methodological Holism

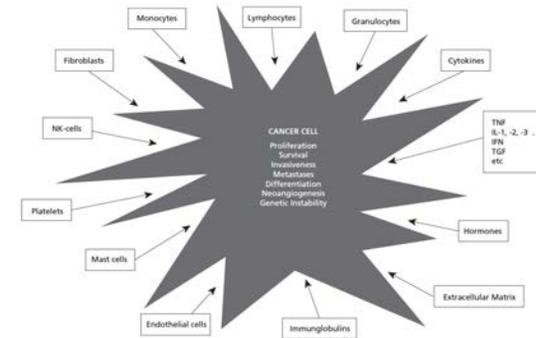
That life can only be understood by studying it as a whole. The world is disordered and it is recognized that each hierarchical level requires its own research strategy not reducible to the methodological strategy below it.

### Epistemological Holism

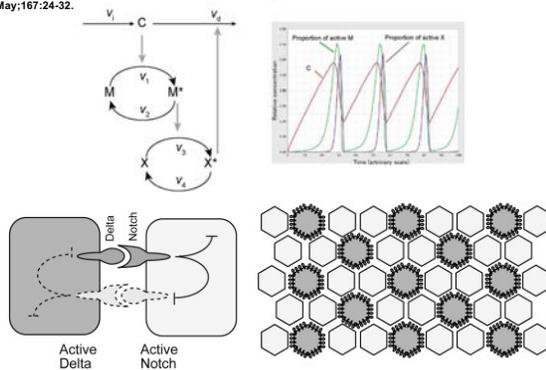
Complex wholes are considered not to be understandable from the mere knowledge of the behavior of the parts in isolation; only properties of the system as a whole may offer understanding.

## From Reductionism to Holism: Systems-oriented Approaches in Cancer Research

Kienle G, Kiene H.  
Glob Adv Health Med. 2012 Nov;1(5):68-77.



"Life-bearing molecules" versus "life-embodying systems": Two contrasting views on the what-is-life (WIL) problem persisting from the early days of molecular biology to the post-genomic cell- and organism-level biology  
Naoki Sato  
Biosystems. 2018 May;167:24-32.



So what do we really mean when we say that systems biology is holistic?

Gatherer D.  
BMC Syst Biol. 2010 Mar 12;4:22.

### Abstract

**Background:** An old debate has undergone a resurgence in systems biology: that of reductionism versus holism. At least 35 articles in the systems biology literature since 2003 have touched on this issue. The histories of holism and reductionism in the philosophy of biology are reviewed, and the current debate in systems biology is placed in context.

**Results:** Inter-theoretic reductionism in the strict sense envisaged by its creators from the 1930s to the 1960s is largely impractical in biology, and was effectively abandoned by the early 1970s in favour of a more piecemeal approach using individual reductive explanations. Classical holism was a stillborn theory of the 1920s, but the term survived in several fields as a loose umbrella designation for various kinds of anti-reductionism which often differ markedly. Several of these different anti-reductionisms are on display in the holistic rhetoric of the recent systems biology literature. This debate also coincides with a time when interesting arguments are being proposed within the philosophy of biology for a new kind of reductionism.

**Conclusions:** Engaging more deeply with these issues should sharpen our ideas concerning the philosophy of systems biology and its future best methodology. As with previous decisive moments in the history of biology, only those theories that immediately suggest relatively easy experiments will be winners.

**Holism, Chinese Medicine and Systems Ideologies: Rewriting the Past to Imagine the Future**

Volker Scheid

In: The Edinburgh Companion to the Critical Medical Humanities. Edinburgh: Edinburgh University Press; 2016 Jun 30. Chapter 3. Wellcome Trust-Funded Monographs and Book Chapters.

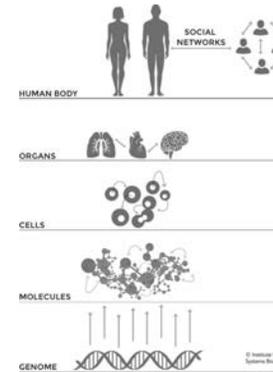
As a Buddhist intellectual, Zhang Taiyan employed the notion of karma as a tool for understanding historical process independent of the ideologies of progress and linear time that the West was then imposing on China. In this view, history is produced by the activity of karmic seeds (業種 *bijia*). These seeds are brought to fruition through action, producing karmic fruits (業果 *vipaka*), which in turn become seeds for new fruits and so on. Existence is perfumed by these seeds, which produce habits that have karmic consequences. This karmic cycle or *samsara* (輪迴 *lunhui*) can only be broken by bringing into awareness and then transcending the conditioning brought forth by the karmic seeds.

The continued presence of non-modern practices like Chinese medicine in the modern world invariably brings us face to face with precisely the questions that Zhang Taiyan sought to resolve. They have not yet been rendered obsolete as tradition, nor have they been completely assimilated to the modern. It is therein that their value lies. The interdisciplinary orientation and openness to constant redefinition the medical humanities claim for themselves make it an ideal space in which critique of the kind inspired by Zhang Taiyan or Max Horkheimer may be enacted. The possibility for doing so, however, depends on the discipline's willingness to engage critically with its own karmic seeds and their fruits. If the medical humanities truly intend to become a space for critique rather than mere criticism, its practitioners will need to find ways of moving beyond the modern constitution that defines and constrains them, not least through their one-sided attachment to biomedicine.

The present chapter argues that opening ourselves up to non-modern medical traditions, not as objects of inquiry but as resources for thinking critically about the fundamental issues of our time, presents an opportunity for doing precisely that.

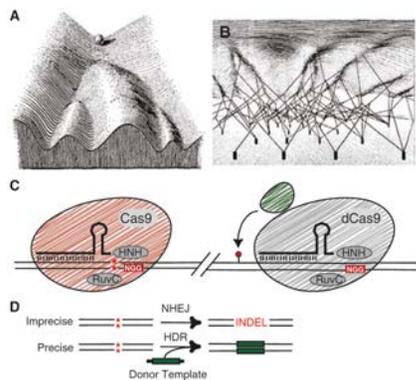
**The new holism: P4 systems medicine and the medicalization of health and life itself**

Vogt H, Hofmann B, Getz L. Med Health Care Philos. 2016 Jun;19(2):307-23.



**From Reductionism to Holism: Toward a More Complete View of Development Through Genome Engineering**

Rebecca K Delker and Richard S Mann  
Adv Exp Med Biol. 2017;1016:45-74.



**Complexity and the reductionism-holism debate in systems biology**

Fulvio Mazzocchi  
Wiley Interdiscip Rev Syst Biol Med. Sep-Oct 2012;4(5):413-27.

**TABLE 1** | An Adapted Version of the Huang's Polarized Scheme for Categorizing Systems Biology (Ref 62, p. 280)

	Localist view	Globalist view
Precursors	<ul style="list-style-type: none"> <li>Classical molecular biology</li> </ul>	<ul style="list-style-type: none"> <li>General network; Kauffman<sup>115</sup></li> </ul>
Mainstream focus	<ul style="list-style-type: none"> <li>Gene- and pathway-centric</li> <li>Large datasets of components parts</li> </ul>	<ul style="list-style-type: none"> <li>Network-centric</li> <li>General principles of complex systems</li> </ul>
Hypothesis level	<ul style="list-style-type: none"> <li>Hypothesis at level of individual pathways</li> </ul>	<ul style="list-style-type: none"> <li>System-level hypothesis</li> </ul>
Philosophical background	<ul style="list-style-type: none"> <li>Reductionism</li> <li>Complicatedness of systems</li> <li>System's properties are placed in the properties of the component parts</li> </ul>	<ul style="list-style-type: none"> <li>Holism</li> <li>Complexity of systems</li> <li>System's properties emerge from collective behavior of the component parts</li> </ul>
Practical aims of investigation	<ul style="list-style-type: none"> <li>To describe thoroughly the biochemistry of individual pathways and their functions</li> <li>To portray idiosyncrasy</li> </ul>	<ul style="list-style-type: none"> <li>To understand general features of genome-scale networks</li> <li>To account universality</li> </ul>
Usual (nonbiologist) partners	<ul style="list-style-type: none"> <li>Computer scientists, engineers</li> </ul>	<ul style="list-style-type: none"> <li>Physicists</li> </ul>



### Hierarchy, determinism, and specificity in theories of development and evolution

Ute Deichmann<sup>1</sup>

Published online: 16 October 2017  
 © Springer International Publishing AG 2017

**Abstract** The concepts of hierarchical organization, genetic determinism and biological specificity (for example of species, biologically relevant macromolecules, or genes) have played a crucial role in biology as a modern experimental science since its beginnings in the nineteenth century. The idea of genetic information (specificity) and genetic determination was at the basis of molecular biology that developed in the 1940s with macromolecules, viruses and prokaryotes as major objects of research often labelled “reductionist”. However, the concepts have been marginalized or rejected in some of the research that in the late 1960s began to focus additionally on the molecularization of complex biological structures and functions using systems approaches. This paper challenges the view that ‘molecular reductionism’ has been successfully replaced by holism and a focus on the collective behaviour of cellular entities. It argues instead that there are more fertile replacements for molecular ‘reductionism’, in which genomics, embryology, biochemistry, and computer science intertwine and result in research that is as exact and causally predictive as earlier molecular biology.

**Table 1. Comparison of features for revolutionary and evolutionary systems biology**

Revolutionary systems biology	Evolutionary systems biology
1. Holism	Reductionism
2. Top-down causation	Bottom-up causation
3. Epigenetics	Genetic determinism
4. Emergentism	Mechanism
5. Synergism	Synthesis
6. Robustness	Homeostasis
7. Nonlinear dynamics	Linear stasis

### Genetic Determinism

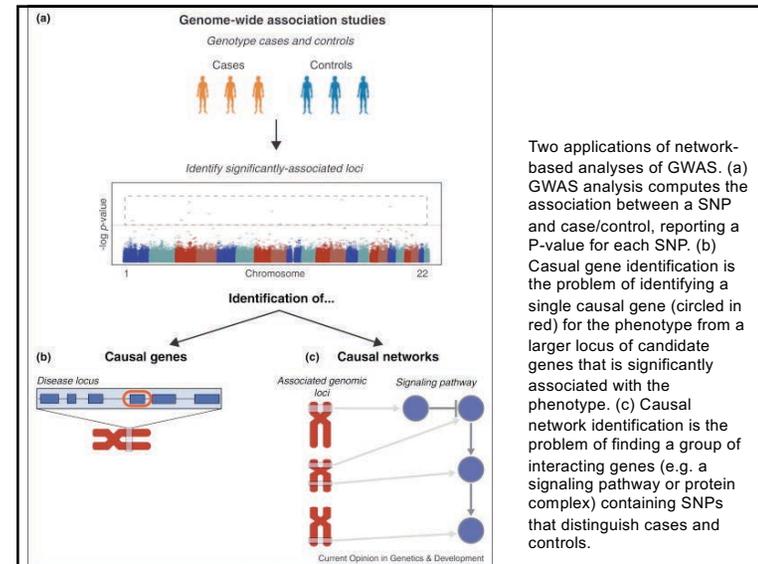
The view that genes (genotype) cause traits (phenotype)

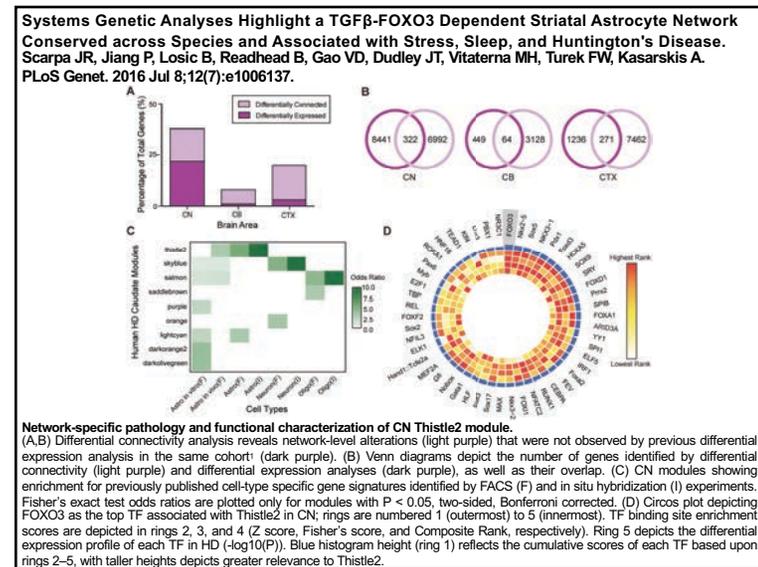
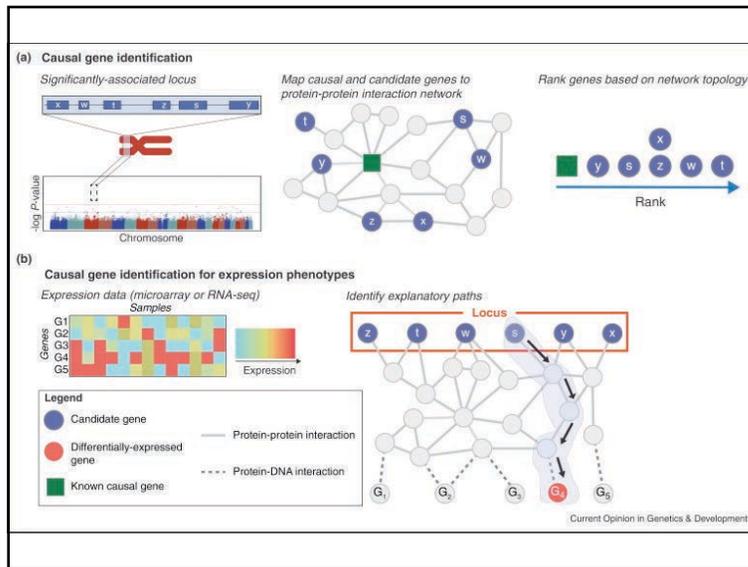
Genetic determinism also referred to as- Geneticism, Genetic Essentialism and Genetic Fatalism

Strong Genetic Determinism- genotype “always” dictates phenotype

Weak Genetic Determinism- genotype “sometimes” dictates phenotype, also potentials or predispositions

Classical Genetics (Mendel) to Molecular Genetics (DNA) to Molecular Biology





**Weight Stigma Reduction and Genetic Determinism.**  
 Hilbert A.  
*PLoS One.* 2016 Sep 15;11(9):e0162993.

**Abstract**

One major approach to weight stigma reduction consists of decreasing beliefs about the personal controllability of-and responsibility for-obesity by educating about its biogenetic causes. Evidence on the efficacy of this approach is mixed, and it remains unclear whether this would create a deterministic view, potentially leading to detrimental side-effects. Two independent studies from Germany using randomized designs with delayed-intervention control groups served to (1) develop and pilot a brief, interactive stigma reduction intervention to educate N = 128 university students on gene × environment interactions in the etiology of obesity; and to (2) evaluate this intervention in the general population (N = 128) and determine mechanisms of change. The results showed (1) decreased weight stigma and controllability beliefs two weeks post-intervention in a student sample; and (2) decreased internal attributions and increased genetic attributions, knowledge, and deterministic beliefs four weeks post-intervention in a population sample. Lower weight stigma was longitudinally predicted by a decrease in controllability beliefs and an increase in the belief in genetic determinism, especially in women. The results underline the usefulness of a brief, interactive intervention promoting an interactionist view of obesity to reduce weight stigma, at least in the short term, lending support to the mechanisms of change derived from attribution theory. The increase in genetic determinism that occurred despite the intervention's gene × environment focus had no detrimental side-effect on weight stigma, but instead contributed to its reduction. Further research is warranted on the effects of how biogenetic causal information influences weight management behavior of individuals with obesity.

**After geneticization.**  
 Arribas-Ayllon M.  
*Soc Sci Med.* 2016 Jun;159:132-9.

**Abstract**

The concept of geneticization belongs to a style of thinking within the social sciences that refers to wide-ranging processes and consequences of genetic knowledge. Lippman's original use of the term was political, anticipating the onerous consequences of genetic reductionism and determinism, while more recent engagements emphasise the productivity and heterogeneity of genetic concepts, practices and technologies. This paper reconstructs the geneticization concept, tracing it back to early political critiques of medicine. The argument is made that geneticization belongs to a style of constructionist thinking that obscures and exaggerates the essentializing effects of genetic knowledge. Following Hacking's advice, we need a more literal sense of construction in terms of 'assembly' to give a clearer account of the relationship between processes and products. Using the 'assemblage' concept to explore the social ontology of genetics, the paper reviews three areas of the empirical literature on geneticization - disease classification, clinical practice and biosociality - to show that a new style of thinking has appeared within the social sciences. In the final assessment, the conditions that gave rise to geneticization are now obsolete. While it may serve as a useful ritual of debate, conceptually geneticization offers a limited account of the heterogeneity of socio-technical change.



**Table 1. Comparison of features for revolutionary and evolutionary systems biology**

Revolutionary systems biology	Evolutionary systems biology
1. Holism	Reductionism
2. Top-down causation	Bottom-up causation
3. Epigenetics	Genetic determinism
4. Emergentism	Mechanism
5. Synergism	Synthesis
6. Robustness	Homeostasis
7. Nonlinear dynamics	Linear stasis

## Mechanism and Emergence

Mechanism-

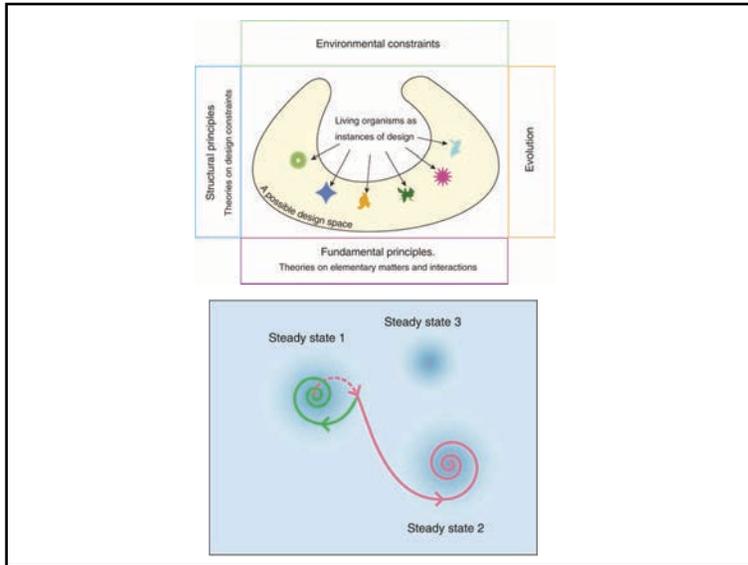
Glennan 2002- "is a complex system that produces that behavior by the interaction of a number of parts, where the interactions between parts can be characterized by direct, invariant, change relating generalizations"

Machamer, Darden, Craver 2000- "are intities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions" (A to B to C)

Mechanisms are especially open to investigation particularly through experimentation

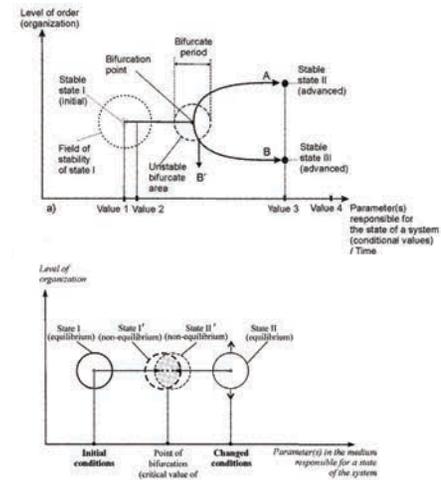
Emergence. Complex systems display properties, often called "emergent properties," that are not demonstrated by their individual parts and cannot be predicted even with full understanding of the parts alone. For example, understanding the properties of hydrogen and oxygen does not allow us to predict the properties of water. Life is an example of an emergent property. It is not inherent in DNA, RNA, proteins, carbohydrates, or lipids but is a consequence of their actions and interactions. A comprehensive understanding of such emergent properties requires systems-level perspectives and cannot be gleaned from simple reductionist approaches.

"What is the difference between a live cat and a dead one? One scientific answer is systems biology. A live cat is the emergent behavior of the system incorporating those parts."



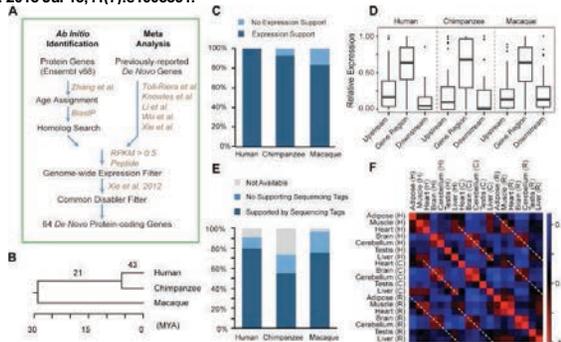
**Emergence of biological organization through thermodynamic inversion.**  
 Kompanichenko V.

Front Biosci (Elite Ed). 2014 Jan 1;6:208-24.



**Emergence, Retention and Selection: A Trilogy of Origination for Functional De Novo Proteins from Ancestral LncRNAs in Primates.**

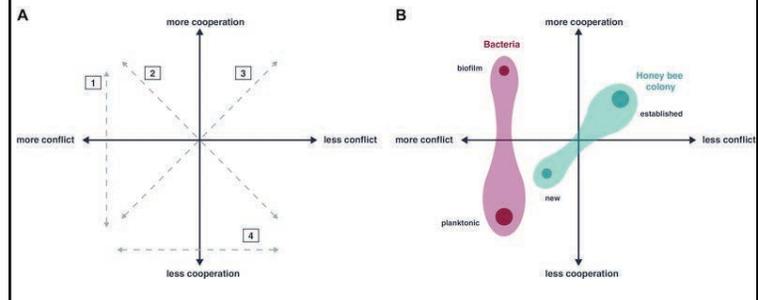
Chen JY, Shen QS, Zhou WZ, et al. PLoS Genet. 2015 Jul 15;11(7):e1005391.



**De novo protein-coding genes originating from lncRNAs.** (A) Computational pipeline for *ab initio* identification and meta-analysis of de novo genes in the hominoid lineage. (B) Number of *de novo* genes on the phylogenetic tree, with the branch length proportional to the divergence time. (C) Stacked histogram showing the percentage of *de novo* gene orthologs that also show expression in chimpanzee or rhesus macaque. (D) Boxplot showing relative expression levels of the transcripts and their nearby regions corresponding to de novo genes (orthologs) in human (chimpanzee or macaque). The nearby regions are defined as upstream and downstream regions with equal length to the corresponding genes. For each region, the relative expression was calculated by normalizing the expression level of this region with the sum of the expression levels of the geneic region and the nearby regions. (E) Percentage of splicing junctions with supporting RNA-Seq reads in human, chimpanzee and rhesus macaque. (F) For each pair of tissues, Spearman correlation coefficients were computed separately, and the extent of tissue-specific differences in de novo gene expressions are shown (based on the color scale). Dotted lines highlight parallel comparisons between two different species.

**Contextual organismality: Beyond pattern to process in the emergence of organisms.**

Diaz-Muñoz SL, Boddy AM, Dantas G, Waters CM, Bronstein JL. Evolution. 2016 Dec;70(12):2669-2677.



The cooperation-conflict space is useful to visualize and evaluate potentially organismal interactions. Panel (A) illustrates organismality space (after Queller and Strassmann 2009) and some of the potential paths (numbered 1–4) organisms can move through under changing ecological contexts, such as development, resource availability, population size, and species interactions. In Panel (B), we provide examples of movement across organismal space in honey bee colonies (blue) and groups of microbial cells (red). In both examples, the cloud plot depicts the movement over “organismality space” and the labels represent the context that facilitates this change. The shading around the points is meant to convey the possibility of small changes in cooperation-conflict in any context.

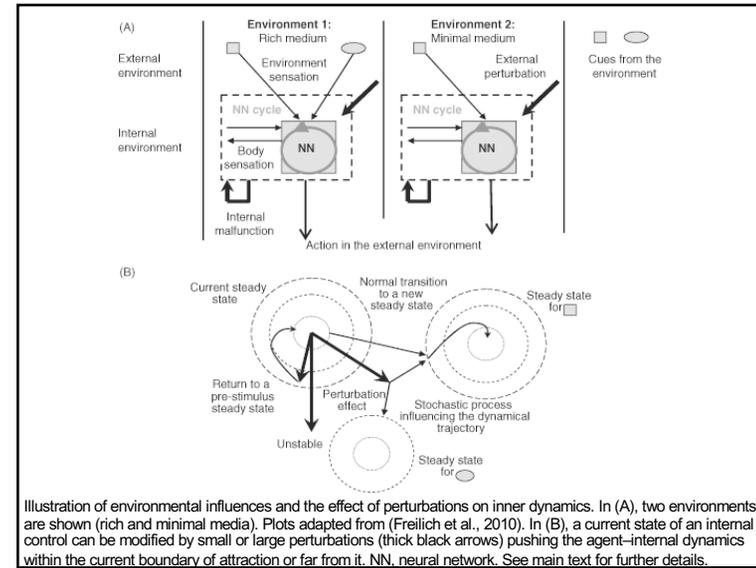
## Homeostasis vs Robustness

### Homeostasis-

Claude Bernard (1800s)- “internal milieu’ s constancy”

Cannon (1939)- “steady states in the body.....a condition that may vary, but is relatively constant”

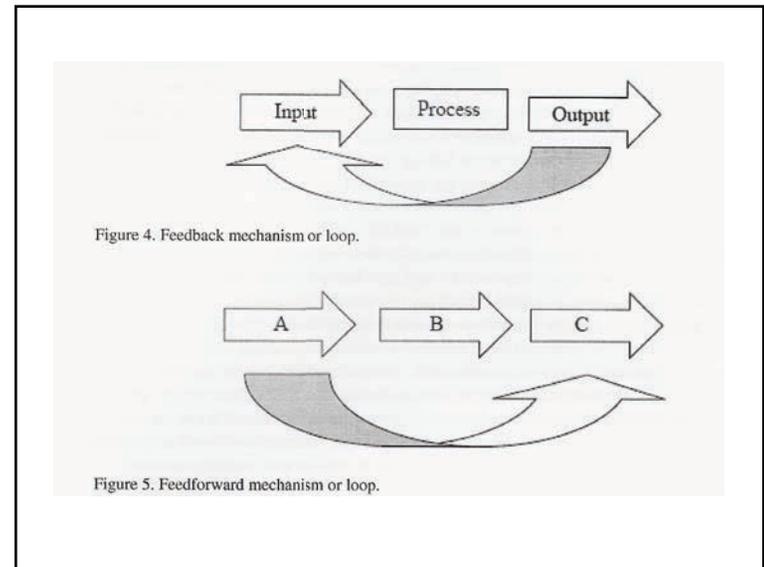
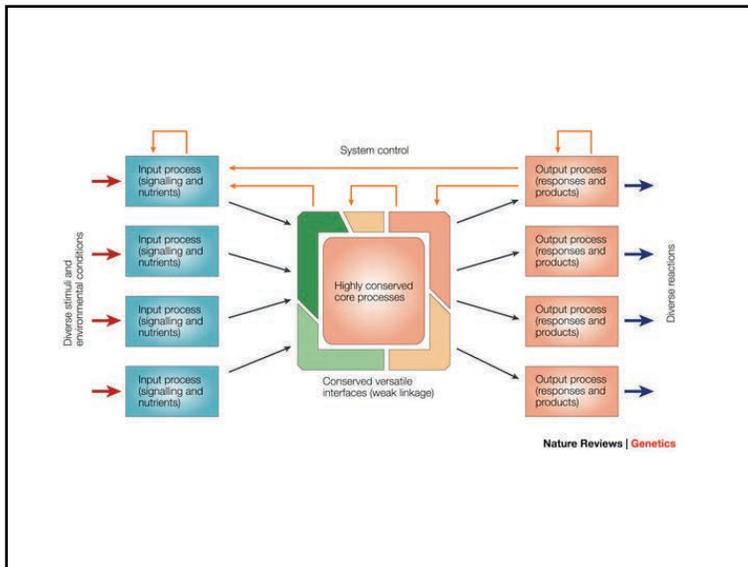
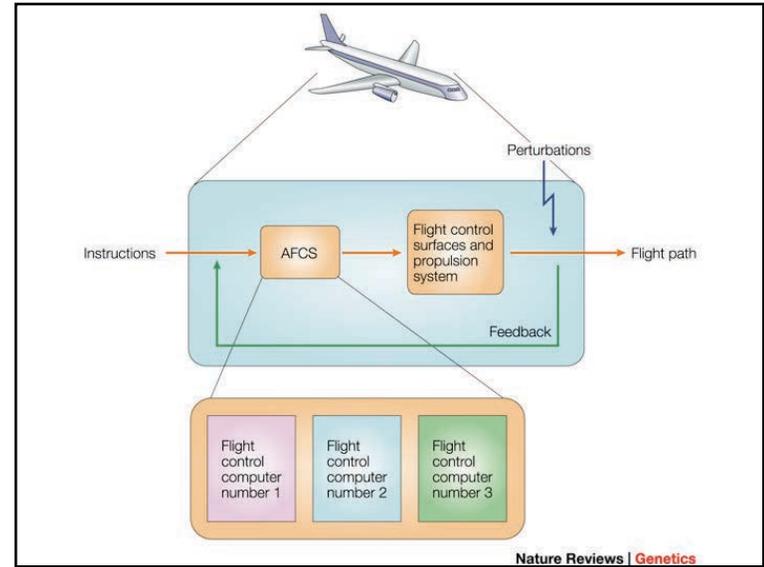
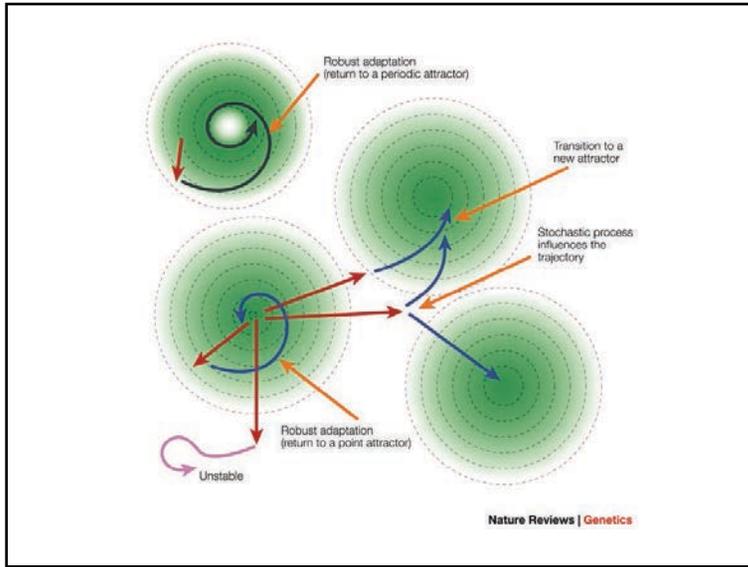
Miglani (2006)- “a mechanism for promoting the stability of phenotypic expression of a genotype when grown over a wide range of environments”

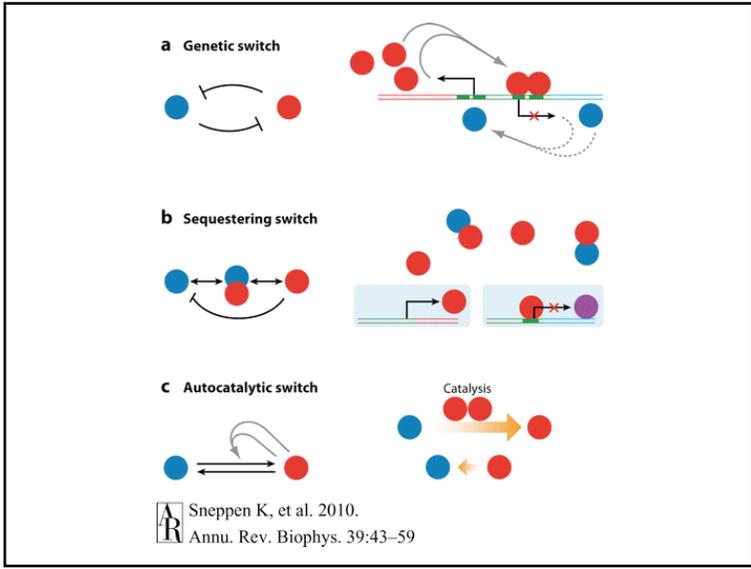
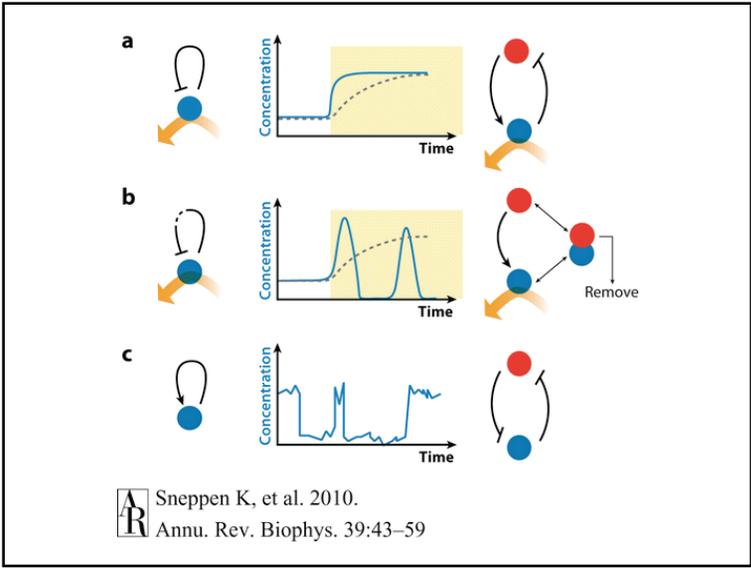
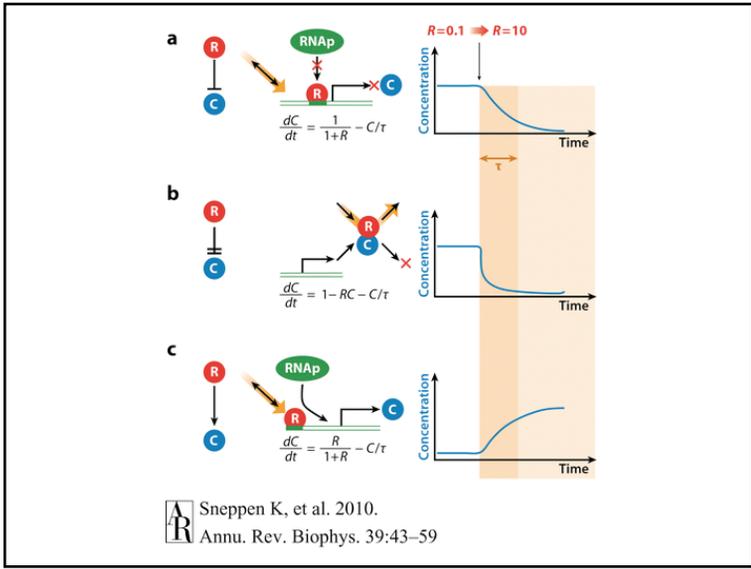
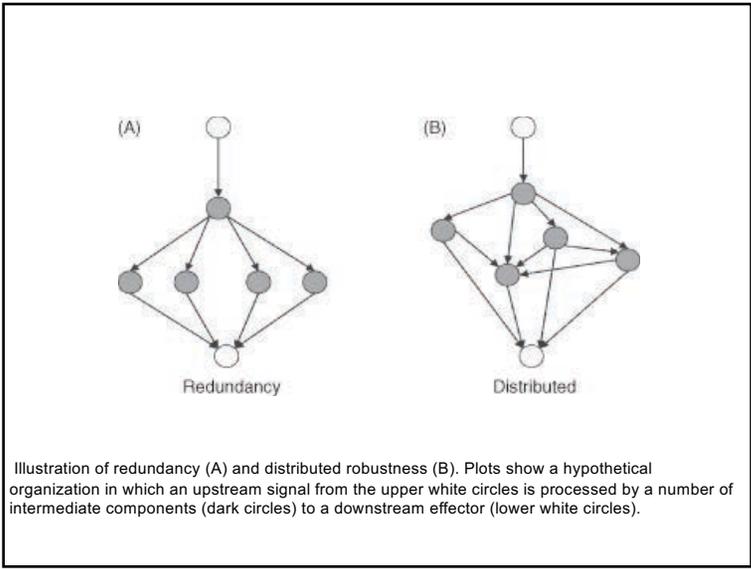


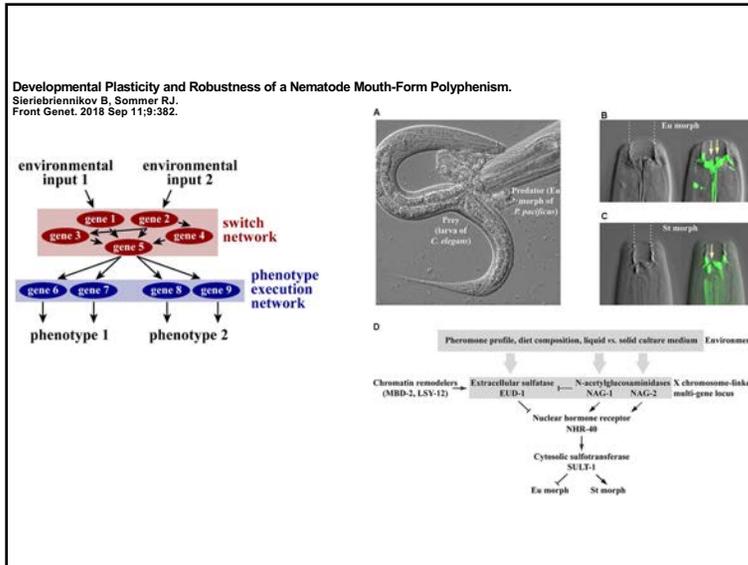
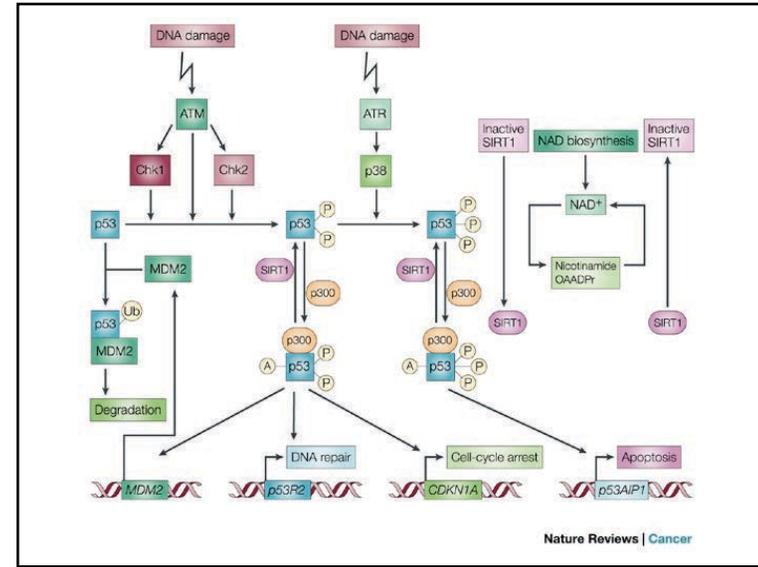
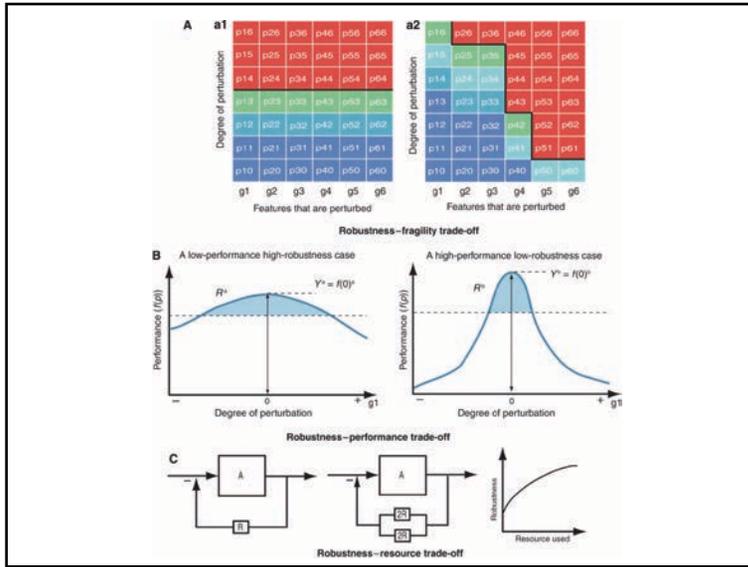
Robustness. Biological systems maintain phenotypic stability in the face of diverse perturbations imposed by the environment, stochastic events, and genetic variation. Robustness often arises through positive and negative feedback loops and other forms of control that constrain a gene’s output. This feedback insulates the system from fluctuations imposed on it by the environment. Positive feedback, in general, enhances sensitivity, whereas negative feedback can dampen noise and reject perturbations. Robustness is an inherent property of all biological systems and is strongly favored by evolution.

### Robustness as an organizational principle

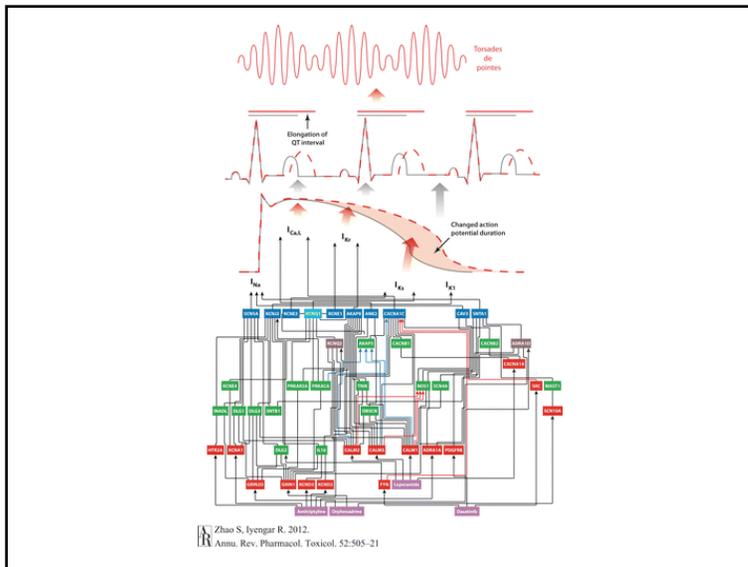
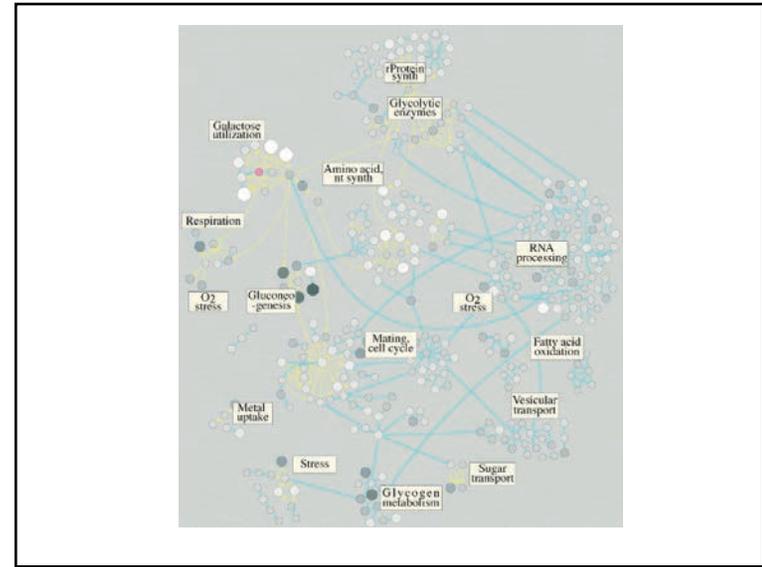
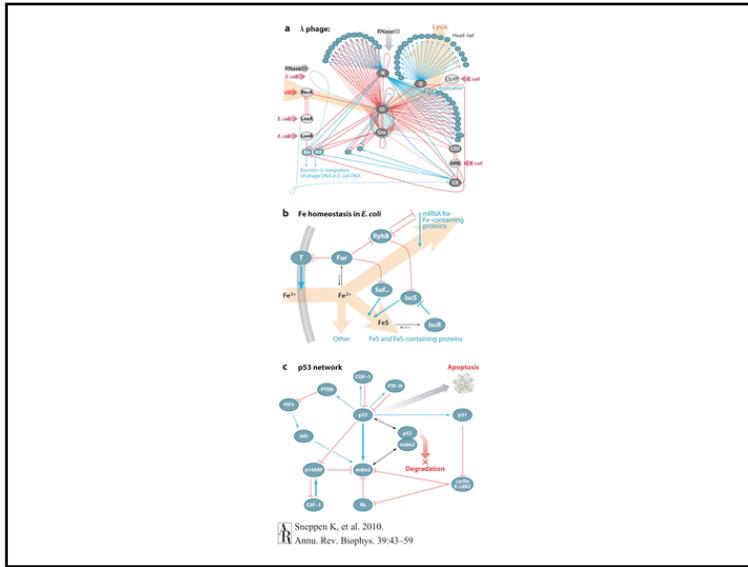
Robustness enables the system to maintain its functionalities against external and internal perturbations. This property has been widely observed across many species, from the level of gene transcription to the level of systemic homeostasis.







Modularity. A further characteristic of complex systems is their modularity. Multiple useful definitions of a module exist. To an engineer, a module is a functional unit, a collection of parts that interact together to perform a distinct function. Such a module would have distinct inputs, things it is sensitive to, and outputs, things it controls. To a biologist, a module in a network is a set of nodes that have strong interactions and a common function. Modularity can contribute to both robustness of the entire system, by confining damage to separable parts, and to evolution, by simply rewiring modules. Furthermore, modularity decreases the risk of failure of the system by preventing the spread of damage in one part of the network throughout the entire network.

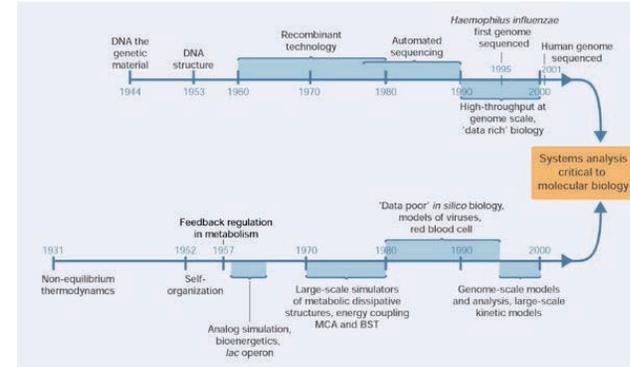


**Table 1. Comparison of features for revolutionary and evolutionary systems biology**

Revolutionary systems biology	Evolutionary systems biology
1. Holism	Reductionism
2. Top-down causation	Bottom-up causation
3. Epigenetics	Genetic determinism
4. Emergentism	Mechanism
5. Synergism	Synthesis
6. Robustness	Homeostasis
7. Nonlinear dynamics	Linear stasis

**Table 1.** Categorisations of systems biology

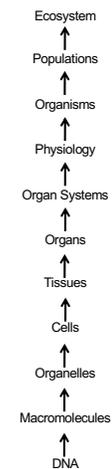
	Type One	Type Two
Haubelt et al., 2000 <sup>(27)</sup>		
Label	Biological systems biology	Systems-oriented biology
Precursors	Reductionist molecular biology	Cybernetics; network theory in electronics; biochemical systems theory (BST) and metabolic control analysis (MCA); cell biology
Focus	Integration of data from different levels & sources	System functions and properties
Huang, 2003 <sup>(11)</sup>		
Label	Localists	Globalists
Precursors	Classical molecular biology	General networks (physics perspective); Kauffman <sup>(28)</sup>
Focus	Large datasets of constituent parts; 'pathway-centric'	Deeper principles of complex systems; wholes
Levesque & Benfey, 2004 <sup>(29)</sup>		
Label	Panoradists	Dynamicists
Precursors	Reductionist molecular biology; genomics	Systems theory
Focus	Components; reconstruction of networks from high-throughput data	Modelling networks as complex systems; applying principles of systems theory
Westerhoff & Palsson, 2004 <sup>(26)</sup>		
Label	Biology-rooted systems biology	Systems-rooted biology
Precursors	Mainstream molecular biology; genomics	Non-equilibrium thermodynamics; self-organisation; BST & MCA
Focus	Pattern recognition and phenomenological modelling of macromolecular interactions	New functional states arising from simultaneous interactions of multiple molecules; fundamental principles and laws



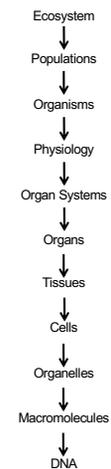
**Table 1.** Comparison of features for revolutionary and evolutionary systems biology

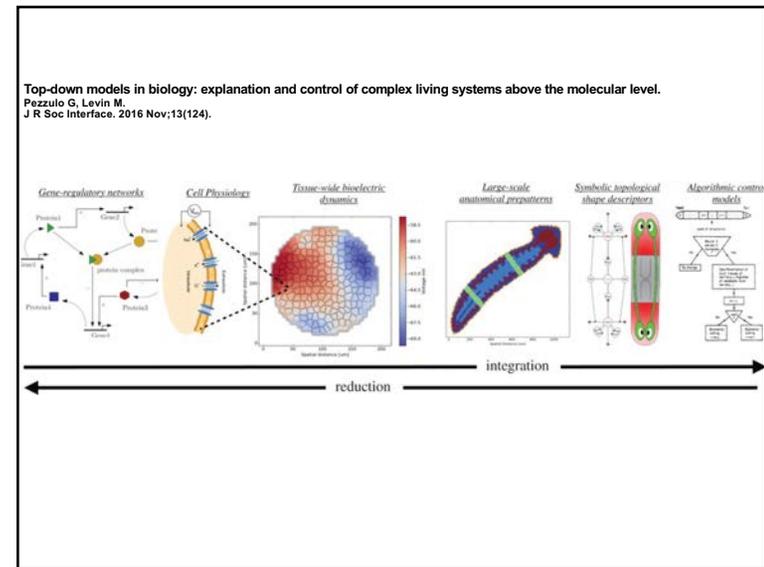
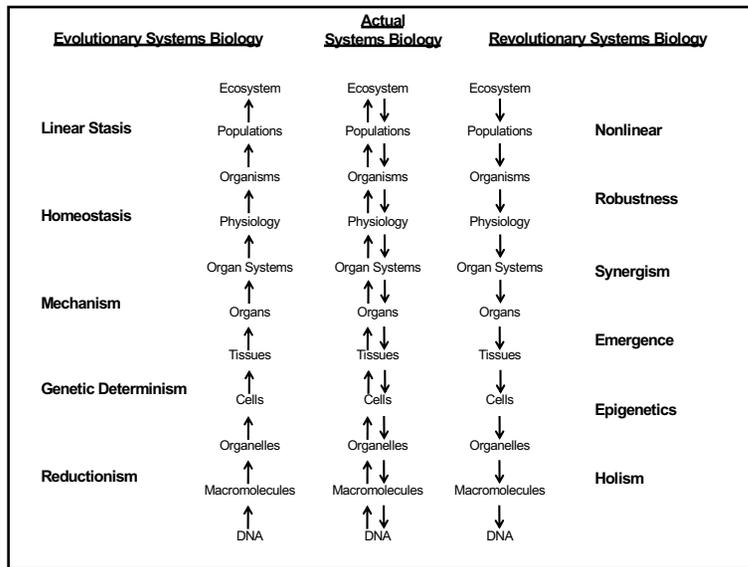
Revolutionary systems biology	Evolutionary systems biology
1. Holism	Reductionism
2. Top-down causation	Bottom-up causation
3. Epigenetics	Genetic determinism
4. Emergentism	Mechanism
5. Synergism	Synthesis
6. Robustness	Homeostasis
7. Nonlinear dynamics	Linear stasis

**Evolutionary Systems Biology**



**Revolutionary Systems Biology**





**“Epigenetics and Systems Biology”**

**Spring 2021 (Odd Years)**  
**Biol 476/576**

**Schedule/Lecture Outline**

Week 1	(Lesson 1)	Systems Biology (History/ Definitions/ Theory)
Week 2	(Lesson 2)	Systems Biology (Networks & Emergence)
Week 3	(Lesson 3)	Systems Biology (Components: DNA to Phenotype)
Week 4	(Lesson 4)	Systems Biology (Genomics / Technology)
Week 5	(Lesson 5)	Epigenetics (History / Molecular Processes)
Week 6	(Lesson 6)	Epigenetics (Molecular Processes & Integration)
Week 7	(Lesson 7)	Epigenetics (Genomics and Technology)
Week 8	(Lesson 8)	Cell & Developmental Biology
Week 9	(Lesson 9)	Epigenetics of Cell & Developmental Biology
Week 10	(Lesson 10)	Environmental Impact on Biology
Week 11	(Lesson 11)	Environmental Epigenetics
Week 12	(Lesson 12)	Disease Etiology
Week 13	(Lesson 13)	Epigenetics & Disease Etiology
Week 14	(Lesson 14)	Evolutionary Biology & Genetics
Week 15	(Lesson 15)	Epigenetics & Evolutionary Biology
Week 16	(Lesson 16)	Grant Review/ Study Section Meeting

Spring 2021- Epigenetics and Systems Biology  
 Lecture Outline - Systems Biology  
 Michael K. Skinner - Biol 476/576  
 10:35-11:50 am, Tuesdays & Thursdays  
 January, 2021  
 Weeks 1 and 2

**Systems Biology**

- History and Definitions
- Reductionism/ Genetic Determination
- Holism/ Emergentism/ Homeostasis or Robustness
- Revolutionary and Evolutionary Systems Biology
- Networks and Computational Biology
- Basic Molecular and Cellular Components

**Required Reading**

Knepper et al. (2014) Systems biology versus reductionism in cell physiology. Am J Physiol Cell Physiol 307:C308-C309.

Wolfe CT. Chance between holism and reductionism: tensions in the conceptualisation of Life. Prog Biophys Mol Biol. 2012 Sep;110(1):113-20.

Zupanic A, Bernstein HC, Heiland I. Systems biology: current status and challenges. Cell Mol Life Sci. 2020 Feb;77(3):379-380.

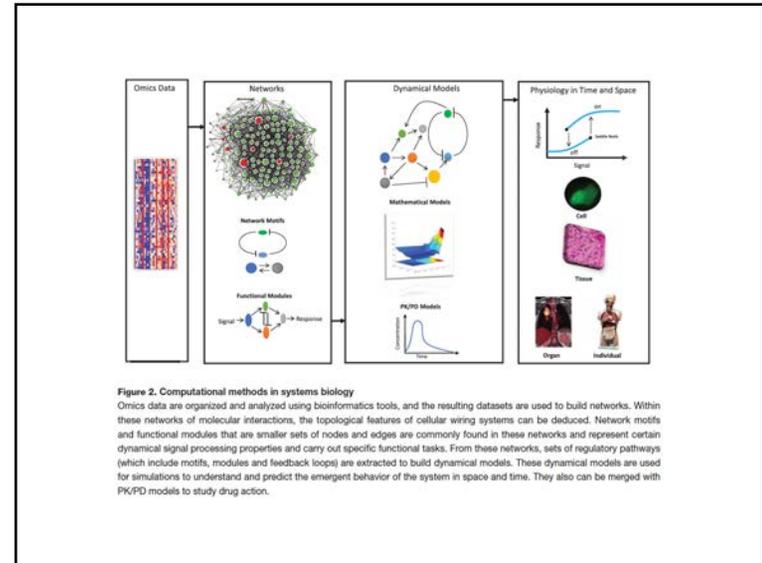
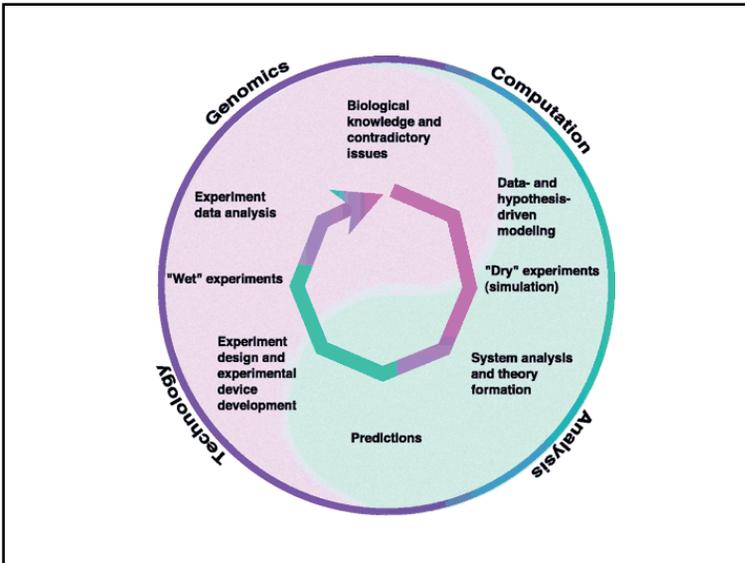
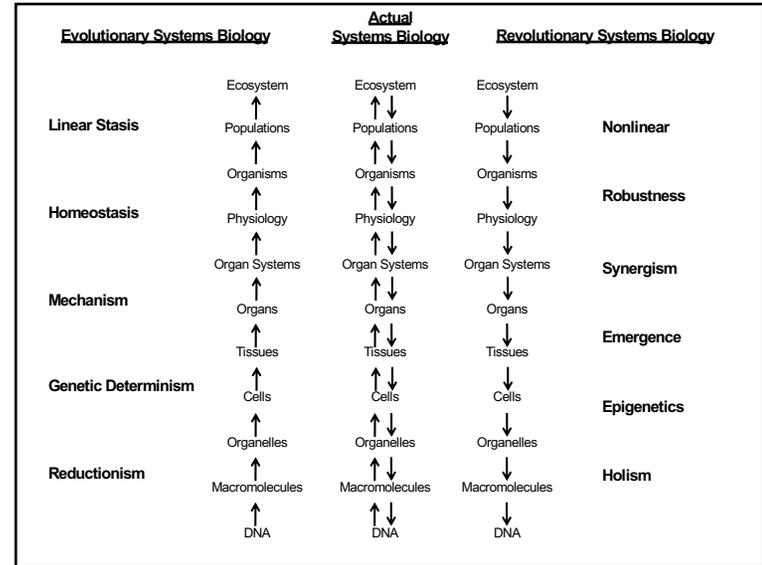
**Background Book References**

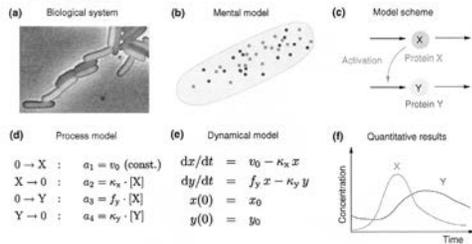
James A. Marcum (2009) *The Conceptual Foundations of Systems Biology*, Nova Science Publishers, Inc.

Eberhard Voit (2012) *A First Course in Systems Biology*, Garland Science

Capra and Luisi (2014) *The Systems View of Life*, Cambridge University Press.

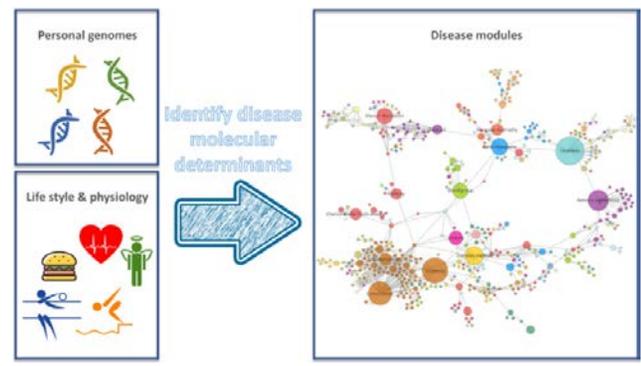
Leonie Ringrose (2017) *Epigenetics and Systems Biology*, Academic Press





**Figure 1.2** Typical abstraction steps in mathematical modeling. (a) *Escherichia coli* bacteria produce thousands of different proteins. If a specific protein type is fluorescently labeled, cells glow under the microscope according to the concentration of this enzyme (Courtesy of M. Elowitz). (b) In a simplified mental model, we assume that cells contain two enzymes of interest, X (red) and Y (blue) and that the molecules (dots) can freely diffuse within the cell. All other substances are disregarded for the sake of simplicity. (c) The interactions between the two protein types can be drawn in a wiring scheme: each protein can be produced or degraded (black arrows). In addition, we assume that proteins of type X can increase the production of protein Y. (d) All individual processes to be considered are listed together with their rates  $a_i$  (occurrence per time). The mathematical expressions for the rates are based on a simplified picture of the actual chemical processes. (e) The list of processes can be translated into different sorts of dynamic models; in this case, deterministic rate equations for the protein concentrations  $x$  and  $y$ . (f) By solving the model equations, predictions for the time-dependent concentrations can be obtained. If these predictions do not agree with experimental data, it indicates that the model is wrong or too much simplified. In both cases, it has to be refined.

**A paradigm shift in medicine: A comprehensive review of network-based approaches**  
 Conte F, Fiscon G, Licursi V, Bizzarri D, D'Antò T, Farina L, Paci P.  
 Biochim Biophys Acta Gene Regul Mech. 2020 Jun;1863(6):194416.



## Computational Biology

- Mathematical modeling
- Data set analysis to develop models

## Computational Models

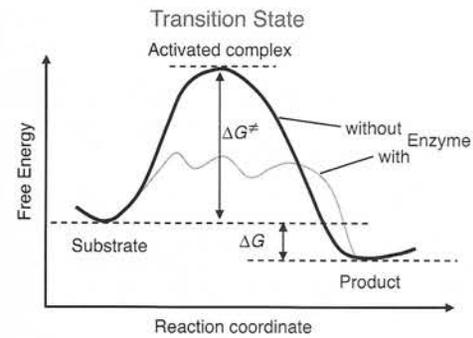
- Model Scope (mathematical elements)
- Model Statement (equations)
- System State (dynamic, snapshot)
- Variables, Parameters and Constants
- Model Behavior (environmental and internal processes)
- Model Assignment (biology described mathematical)
- Data Integration (omics data)

1.3.6

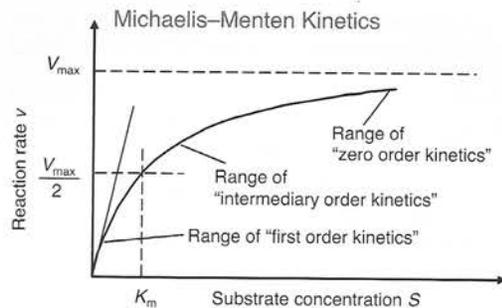
Model Classification

For modeling, processes are classified with respect to a set of criteria.

- A structural or *qualitative* model (e.g., a network graph) specifies the interactions among model elements. A *quantitative* model assigns values to the elements and to their interactions, which may or may not change.
- In a *deterministic* model, the system evolution through all following states can be predicted from the knowledge of the current state. *Stochastic* descriptions give instead a probability distribution for the successive states.
- The nature of values that time, state, or space may assume distinguishes a *discrete* model (where values are taken from a discrete set) from a *continuous* model (where values belong to a continuum).
- *Reversible* processes can proceed in a forward and backward direction. Irreversibility means that only one direction is possible.
- *Periodicity* indicates that the system assumes a series of states in the time interval  $\{t, t + \Delta t\}$  and again in the time interval  $\{t + i\Delta t, t + (i + 1)\Delta t\}$  for  $i = 1, 2, \dots$



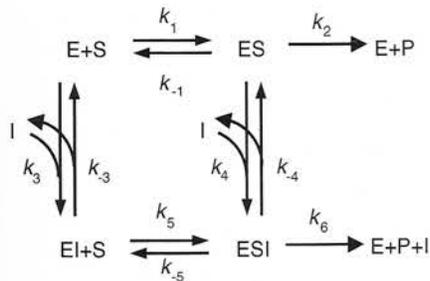
**Figure 2.1** Change of free energy along the course of a reaction. The substrate and the product are situated in local minima of the free energy; the active complex is assigned to the local maximum. The enzyme may change the reaction path and thereby lower the barrier of free energy.



**Figure 2.2** Dependence of reaction rate  $v$  on substrate concentration  $S$  in Michaelis-Menten kinetics.  $V_{max}$  denotes the maximal reaction rate that can be reached for large substrate concentration.  $K_m$  is the substrate concentration that leads to half-maximal reaction rate. For low substrate concentration,  $v$  increases almost linearly with  $S$ , while for high substrate concentrations  $v$  is almost independent of  $S$ .

**Table 2.1** Different approaches for the linearization of Michaelis-Menten enzyme kinetics.

	Lineweaver-Burk	Eadie-Hofstee	Hanes-Woolf
Transformed equation	$\frac{1}{v} = \frac{K_m}{V_{max}} \frac{1}{S} + \frac{1}{V_{max}}$	$v = V_{max} - K_m \frac{v}{S}$	$\frac{S}{v} = \frac{S}{V_{max}} + \frac{K_m}{V_{max}}$
New variables	$\frac{1}{v}$	$\frac{v}{S}$	$\frac{S}{v}$
Graphical representation			



**Figure 2.3** General scheme of inhibition in Michaelis–Menten kinetics. Reactions 1 and 2 belong to the standard scheme of Michaelis–Menten kinetics. Competitive inhibition is given, if in addition reaction 3 (and not reactions 4, 5, or 6) occurs. Uncompetitive inhibition involves reactions 1, 2, and 4, and noncompetitive inhibition comprises reactions 1, 2, 3, 4, and 5. Occurrence of reaction 6 indicates partial inhibition.

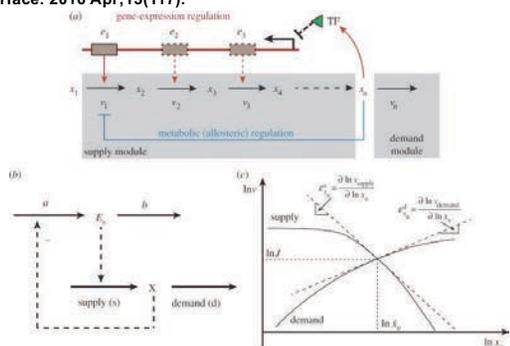
**Table 2.3** Types of inhibition for irreversible and reversible Michaelis–Menten kinetics<sup>a</sup>.

Name	Implementation	Equation – irreversible case	Equation – reversible case	Characteristics
Competitive inhibition	I binds only to free E; P-release only from ES complex; $k_{-3} = k_{-4} = k_4 = 0$	$v = \frac{V_{max}S}{K_m + S}$	$v = \frac{V_{max}(S/K_{m0}) - V_{max}^*(P/K_{mP})}{(S/K_{m0}) + (P/K_{mP}) + i_0}$	$K_m$ changes, $V_{max}$ remains same. S and I compete for the binding place; high S may out compete I.
Uncompetitive inhibition	I binds only to the ES complex; P-release only from ES complex; $k_{-3} = k_{-4} = k_4 = 0$	$v = \frac{V_{max}S}{K_m + S + i_0}$	$v = \frac{V_{max}(S/K_{m0}) - V_{max}^*(P/K_{mP})}{i_0 + (S/K_{m0}) + (P/K_{mP}) + i_0}$	$K_m$ and $V_{max}$ change, but their ratio remains same. S may not out compete I.
Noncompetitive inhibition	I binds to E and ES; P-release only from ES; $k_{-3} = k_{-4} = 0$	$v = \frac{V_{max}S}{(K_m + S)(1 + i_0)}$	$v = \frac{V_{max}(S/K_{m0}) - V_{max}^*(P/K_{mP})}{(1 + (S/K_{m0}) + (P/K_{mP}) + i_0)}$	$K_m$ remains, $V_{max}$ changes. S may not out compete I.
Mixed inhibition	I binds to E and ES; P-release only from ES; $k_{-3} \neq k_{-4}, k_4 = 0$	$v = \frac{V_{max}S}{K_m + S + i_0}$		$K_m$ and $V_{max}$ change. $K_{i3} > K_{i4}$ : competitive–noncompetitive inhibition. $K_{i3} < K_{i4}$ : noncompetitive–uncompetitive inhibition.
Partial inhibition	I may bind to E and ES; P-release from ES and ESI; $k_{-3} \neq k_{-4}, k_4 \neq 0$	$v = \frac{V_{max}S(1 + (k_4/k_3)(i_0/K_{i3}))}{K_m + S + i_0}$		$K_m$ and $V_{max}$ change. if $k_4 > k_3$ : activation instead of inhibition.

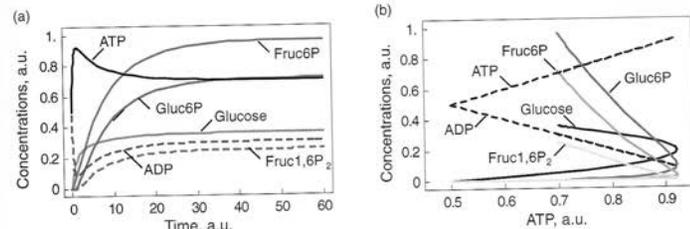
<sup>a</sup>These abbreviations are used:  $K_{i3} = \frac{k_3}{k_{-3}}$ ,  $K_{i4} = \frac{k_4}{k_{-4}}$ ,  $i_0 = 1 + \frac{i}{K_i}$ ,  $i_4 = 1 + \frac{i}{K_{i4}}$ .

### Synthetic biology and regulatory networks: where metabolic systems biology meets control engineering.

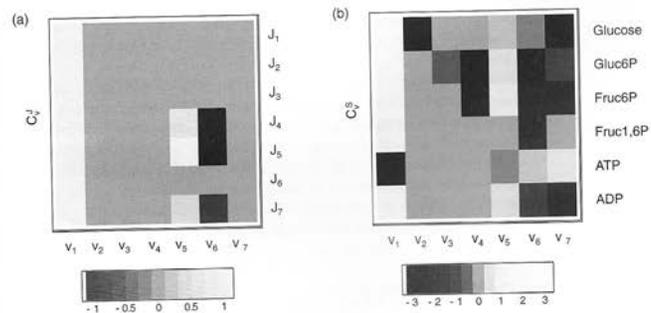
He F, Murabito E, Westerhoff HV. J R Soc Interface. 2016 Apr;13(117).



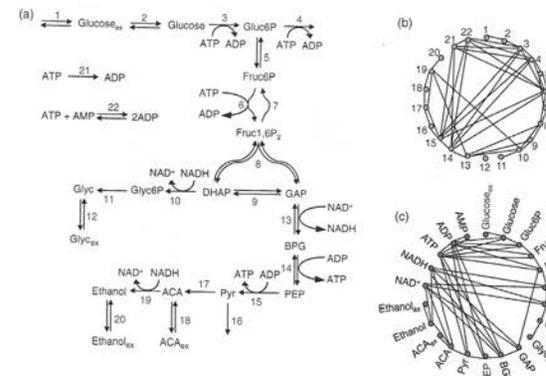
An unbranched metabolic pathway under hierarchical regulation. (a) The first enzyme is regulated through both transcriptional repression and allosteric activity inhibition by the end product. Enzymes in other steps might also be regulated through gene expression (in dashed arrows), but this is not explicitly considered here. TF denotes transcription factor. (b) The hierarchical supply–demand representation of the pathway (a). The lower part represents the classical metabolic supply–demand system, in which only the metabolic regulation (in this case allosteric inhibition) is considered. The letter ‘X’ denotes the penultimate product  $x_n$ , still in pathway. The supply is catalysed by enzyme  $E_6$  (i.e.  $e_6$  here or enzymes stemming from an entire operon). (c) Illustration of the steady-state properties of a supply–demand system in terms of changes in the flux, intermediate concentration and elasticity coefficients.



**Figure 3.3** Dynamic behavior of the upper glycolysis model (Figure 3.2 and Eq. (3.1)). Initial conditions at  $t = 0$ :  $Glucose(0) = Gluc6P(0) = Fruc6P(0) = Fruc-1,6P_2(0) = 0$  and  $ATP(0) = ADP(0) = 0.5$  (arbitrary units). Parameters:  $k_1 = 0.25$ ,  $k_2 = 1$ ,  $k_3 = 1$ ,  $k_4 = 1$ ,  $k_5 = 1$ ,  $k_6 = 1$ , and  $k_7 = 2.5$ . The steady-state concentrations are  $Glucose^{st} = 0.357$ ,  $Gluc-6P^{st} = 0.714$ ,  $Fruc-6P^{st} = 0.964$ ,  $Fruc-1,6P_2^{st} = 0.2$ , and  $ATP^{st} = 0.7$ , and  $ADP^{st} = 0.25$ . The steady-state fluxes are  $J_1 = J_2 = J_3 = J_4 = J_5 = J_6 = 0.25$ ,  $J_4 = 0.5$ , and  $J_7 = 0.75$ . (a) Time-course plots (concentration versus time), (b) phase-plane plot (concentrations versus concentration of ATP with varying time); all curves start at  $ATP = 0.5$  for  $t = 0$ .



**Figure 3.4** Flux and concentration control coefficients for the glycolysis model in Figure 3.2 with the parameters given in the legend of Figure 3.3. Values of the coefficients are indicated in gray-scale: gray means zero control, white or light gray indicates positive control, dark gray or black negative control, respectively.



**Figure 3.5** Full glycolysis models. (a) Main reactions and metabolites, (b) network of reactions connected by common metabolites, (c) network of metabolites connected by common reactions.

#### 4.1 Data for Small Metabolic and Signaling Systems

##### Summary

The mathematical equations that are used to develop kinetic models of biochemical systems are so complex that, except for the most simple cases, it is impossible to solve them analytically. Therefore, numerical simulations are required to predict how concentrations develop over time and when and if the system will reach a steady state. But numerical simulations need numerical data to assign specific values to a large number of molecule properties. Among these properties are Michaelis-Menten constants,  $K_m$ , and maximal velocities,  $V_{max}$ , (for enzymes), but also biological half-lives, binding constants, molecule concentrations, and diffusion rates. In the early days of mathematical modeling, it was very difficult to obtain enough data of sufficient quality to make reliable model predictions. In such a situation, only qualitative models can be constructed that investigate the question if a certain behavior is at all possible or not. Although such a model provides valuable information about a system of biochemical reactions, most models today aim to be quantitative. This means that the model should agree well with measured concentrations and also predictions regarding changes of molecule concentrations are given as specific numbers instead of a qualitative up or down statement. To develop quantitative models, it is therefore essential to obtain a large number of reliable data for the model parameters. One source are specialized databases, which will be discussed in this section. But the process of filling these databases is currently very time-consuming, since most kinetic data have to be extracted by hand from the existing literature. Recently developed experimental techniques aim to improve the situation by enabling researchers to measure large numbers of kinetic data with high accuracy. Some of these techniques will be described at the end of chapter 4.1.

#### 4.2 Parameter Estimation

##### Summary

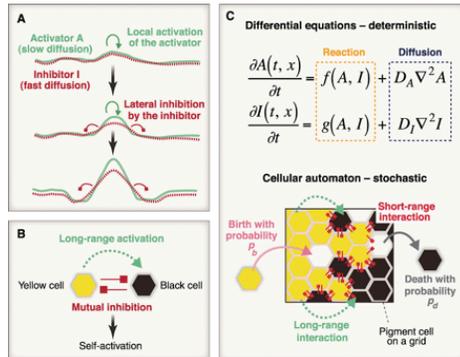
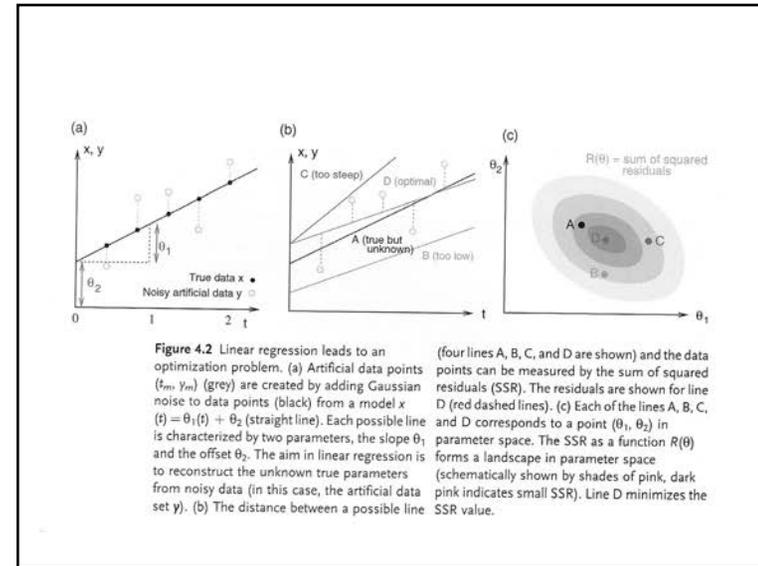
Parameters in a model can be determined by fitting the model to experimental data. In the method of least squares, a common approach in parameter estimation, the sum of squared residuals between model predictions and data is minimized. For data with additive standard Gaussian errors, this method is equivalent to maximum likelihood estimation. The variability of parameter estimates due to noisy and insufficient data can be assessed by repeating the estimation with resampled data ("bootstrapping") and the quality of model predictions can be tested by cross-validation. In Bayesian parameter estimation, parameter sets are scored by how well they agree with both available data and with certain prior assumptions, which are expressed by probability distributions of the parameters. The parameter estimation often leads to minimization problems, which can be solved with a variety of local or

global optimization algorithms. Local optimizers are relatively fast, but they may get stuck in suboptimal local optima. Global optimizers like simulated annealing or genetic algorithms can evade local minima, but they may be numerically demanding.

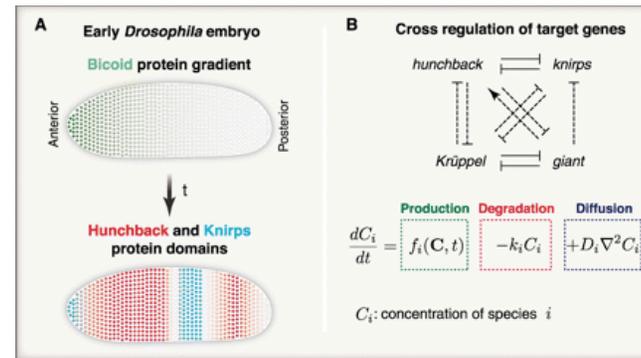
## Parameter Estimations

- Regression (minimum of the function)
- Estimators (distance measure)
- Maximum likelihood estimation (Gaussian noise)
- Identifiability (landscape in parameter space)
- Bootstrapping (sampling and noisy data)
- Cross Validation (model fitting and prediction)
- Bayesian Parameter Estimation (parameter not fixed, random variables)
- Local and Global Optimization
- Machine Learning Algorithms (simulations)

(Mathematica / Matlab / Systems Biology Markup Language, SBML)



Patterning with activator-inhibitor systems. (A) Local activation and lateral inhibition generates spatially heterogeneous patterns. (B) Interactions between black and yellow pigment cells produce Turing patterns in zebrafish skin. Mutual inhibition between them functions as self-activation for the yellow cells. Each yellow cell activates distant black cells. Therefore, inhibition of the yellow cell by the black cell works as a lateral inhibition. (C) Different modeling approaches to spontaneous pattern formation.

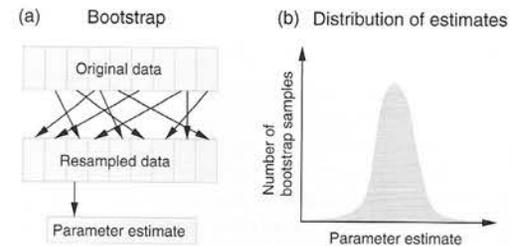


Patterning with signaling gradients. (A) Schematic of early fruit fly embryo showing the maternal gradient of Bicoid protein at cycle 13 that directs the formation of precise target gene domains such as *hunchback* and *knirps*. (B) Proposed gene regulatory network showing cross-regulation of target genes (9). The four genes are also under control of Bicoid and other players.  $t$ , time.

### Parameter Estimations

- Regression (minimum of the function)
- Estimators (distance measure)
- Maximum likelihood estimation (Gaussian noise)
- Identifiability (landscape in parameter space)
- Bootstrapping (sampling and noisy data)
- Cross Validation (model fitting and prediction)
- Bayesian Parameter Estimation (parameter not fixed, random variables)
- Local and Global Optimization
- Genetic Algorithms (simulations)

(Mathematica / Matlab / Systems Biology Markup Language, SBML)

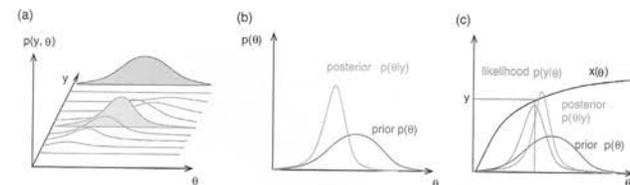


**Figure 4.4** The bootstrapping method. (a) Hypothetical data sets are created by resampling data values from the original data set. Each resampled data set yields a parameter estimate  $\hat{\theta}$ . (b) The distribution of the parameter estimates, obtained from the bootstrap samples, approximates the true distribution of the estimator  $\hat{\theta}$ . A good approximation requires a large original data set.

### Parameter Estimations

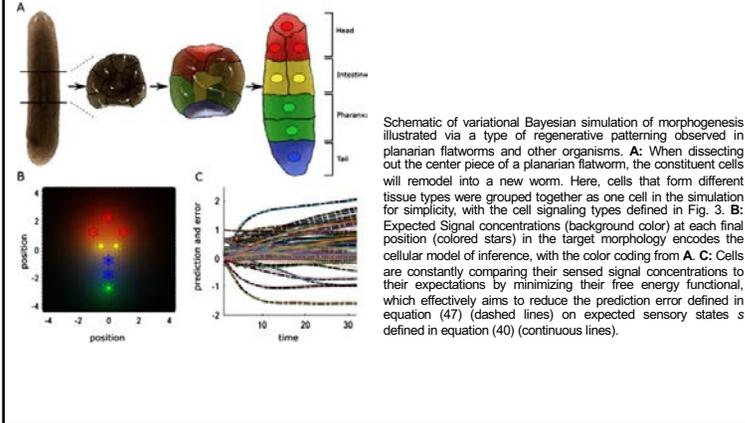
- Regression (minimum of the function)
- Estimators (distance measure)
- Maximum likelihood estimation (Gaussian noise)
- Identifiability (landscape in parameter space)
- Bootstrapping (sampling and noisy data)
- Cross Validation (model fitting and prediction)
- Bayesian Parameter Estimation (parameter not fixed, random variables)
- Local and Global Optimization
- Genetic Algorithms (simulations)

(Mathematica / Matlab / Systems Biology Markup Language, SBML)



**Figure 4.6** Bayesian parameter estimation. (a) In Bayesian estimation, the parameters  $\theta$  and the data  $y$  follow a joint probability distribution with density  $p(y, \theta)$ . The marginal probability density  $p(\theta)$  of the parameters is called the prior (blue), while the conditional density  $p(\theta|y)$  given a certain data set is called the posterior (magenta). (b) The posterior (magenta) is more narrow than the prior (blue), which reflects the information gained by considering the data. (c) Prior, likelihood and posterior. In a model, the data  $y$  are given by a mean prediction  $x(\theta)$  (black line) plus Gaussian noise. An observed value  $y$  gives rise to a likelihood function  $L(\theta|y) = p(y|\theta)$  in parameter space. The posterior is proportional to the product of prior and likelihood function.

**Morphogenesis as Bayesian Inference: A variational approach to pattern formation and control in complex biological systems**  
 Kuchling F, Friston K, Georgiev G, Levin M.  
 Phys Life Rev. 2020 Jul;33:66-108.



### Parameter Estimations

- Regression (minimum of the function)
- Estimators (distance measure)
- Maximum likelihood estimation (Gaussian noise)
- Identifiability (landscape in parameter space)
- Bootstrapping (sampling and noisy data)
- Cross Validation (model fitting and prediction)
- Bayesian Parameter Estimation (parameter not fixed, random variables)
- Local and Global Optimization
- Genetic Algorithms (simulations)

(Mathematica / Matlab / Systems Biology Markup Language, SBML)

### Machine Learning Modeling

- Large data set with manipulations
- Test data set with known outcomes parameters (learning data set)
- Mathematical Algorithm development from training set
- Refine Algorithm development with large data set
- Final Algorithm should be correct with training set and reveal new biology insight

$$x_3 = \frac{k_{11}x_0}{k_{20}x_0} \quad (31)$$

where  $x_1$  and  $x_4$  are the solutions of the nonlinear equations

$$0 = \frac{1}{2} \left( k_3 + k_{13} + \frac{k_1}{k_{21}} (k_3 + k_{13} + k_{14} - k_{12}x_1) \right) \left( x_4 - \frac{k_4 k_1}{k_2 k_5} \right) - k_2 x_1 - \frac{2k_1 k_{12} x_1^2}{k_{20} + k_2} + \frac{k_{12}}{k_{21}} (k_3 + k_{13} + k_{14} - k_{12}x_1) x_4^2 \quad (32)$$

$$0 = k_{10} \left( -\frac{k_{12}}{k_{21}} x_4^2 - \frac{1}{2k_{21}} (k_3 + k_{13}) \left( x_4 - \frac{k_4 k_1}{k_2 k_5} \right) \right) \times$$

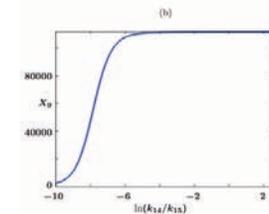
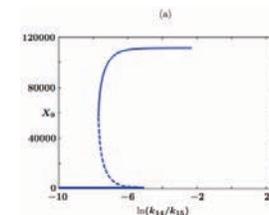
$$\left( \frac{k_1}{k_4} \left( k_2 k_1 x_0 + k_1 k_2 x_0 \frac{k_{12} x_1^2}{k_{20} + k_2} \right) - k_2 x_1 - \frac{2k_1 k_{12} x_1^2}{k_{20} + k_2} \right) \quad (33)$$

$$-k_1 \left( k_2 x_1 + \frac{2k_1 k_{12} x_1^2}{k_{20} + k_2} + \frac{k_{12}}{k_{21}} k_{12} x_1 x_4^2 \right)$$

In the constitutive case, equations (16) and (23) become  $x_2 = k_{12}/k_4$  and equation (33) becomes

$$0 = k_{10} \left( -\frac{k_{12}}{k_{21}} x_4^2 - \frac{1}{2k_{21}} (k_3 + k_{13}) \left( x_4 - \frac{k_4 k_1}{k_2 k_5} \right) \right) \times$$

$$\left( \frac{k_1 k_{12}}{k_4} - k_2 x_1 - \frac{2k_1 k_{12} x_1^2}{k_{20} + k_2} \right) - k_1 \left( k_2 x_1 + \frac{2k_1 k_{12} x_1^2}{k_{20} + k_2} + \frac{k_{12}}{k_{21}} k_{12} x_1 x_4^2 \right) \quad (34)$$



**Bifurcation diagrams for the deterministic reaction rate equations.**

The diagrams are constructed using XPPAUT for equations (1)-(13) and the parameter values given in Results. Numbers of reporter protein molecules produced are plotted against the natural logarithm of the external signal  $\ln(k_{14}/k_{13})$ , in the a) autoregulated and b) constitutive cases, showing a bistable and graded response respectively. Bold lines denote stable solutions and dashed lines denote unstable solutions. doi:10.1371/journal.pcbi.1002396.g003

## Methods of information theory and algorithmic complexity for network biology.

Zenil H, Kiani NA, Tegnér J.  
Semin Cell Dev Biol. 2016 Mar;51:32-43.

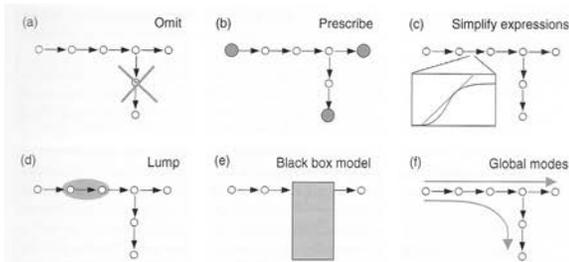
### Abstract

We survey and introduce concepts and tools located at the intersection of information theory and network biology. We show that Shannon's information entropy, compressibility and algorithmic complexity quantify different local and global aspects of synthetic and biological data. We show examples such as the emergence of giant components in Erdős-Rényi random graphs, and the recovery of topological properties from numerical kinetic properties simulating gene expression data. We provide exact theoretical calculations, numerical approximations and error estimations of entropy, algorithmic probability and Kolmogorov complexity for different types of graphs, characterizing their variant and invariant properties. We introduce formal definitions of complexity for both labeled and unlabeled graphs and prove that the Kolmogorov complexity of a labeled graph is a good approximation of its unlabeled Kolmogorov complexity and thus a robust definition of graph complexity.

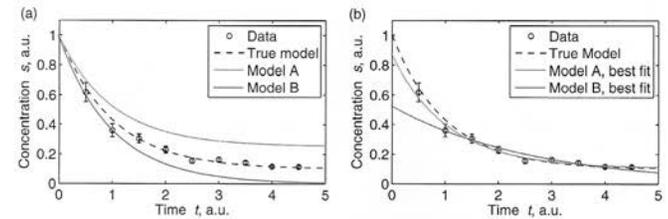
### 4.3 Reduction and Coupling of Models

#### Summary

The aim in model reduction is to simplify complex models, i.e., to capture their key dynamical properties with fewer equations and parameters. This facilitates understanding, numerical and analytical calculations, and model fitting. A reduced model has to emulate the behavior of relevant variables under relevant conditions and on the relevant time scale. To reduce a model, elements can be omitted, lumped, or replaced by effective descriptions, and global model behavior can be approximated by global modes or simplified black-box models. Important simplifying concepts like quasi-equilibrium or quasi-steady state can be justified by a distinction between fast and slow processes. Once models for parts of the cell have been established, they may be combined to form more complex models, which may show new emergent behavior.



**Figure 4.8** Simplifications in biochemical models. The scheme shows a branched pathway of metabolites (circles) and reactions (arrows). (a) Omitting substances or reactions. (b) Predefining the values of concentrations or fluxes or relations between them. (c) Simplifying the mathematical expressions (e.g., omitting terms in a kinetic law, using simplified kinetic laws [21], neglecting insensitive parameters [22]). (d) Lumping the substances, for instance, similar metabolites, protonation states of a metabolite, or metabolite concentrations in different compartments. Likewise, subsequent reactions in a pathway or elementary steps in a reaction can be replaced by a single reaction of the same velocity; for parallel reactions, like the action of isoenzymes, the velocities are summed up; for the two directions of a reaction, the velocities are subtracted. (e) Replacing the model parts by a dynamic black-box model that mimics the input-output behavior [23]. (f) Describing the dynamic behavior by global modes (e.g., elementary flux modes or eigenmodes of the Jacobian).



**Figure 4.15** Fit of the example models. (a) Artificial data (a concentration time series, black dots) were generated by adding Gaussian noise to results of the true model (dashed line). Solid curves show simulations from model A (red) and B (blue) with fixed parameters. (b) After estimating the parameters of models A and B, a better fit is obtained.

Table 4.3 Calculation of selection criteria for the running example.<sup>a</sup>

	$\sigma$ large		$\sigma$ small	
	Model A	Model B	Model A	Model B
$n$	3	2	–	–
$k$	9	9	–	–
$2k$	6	4	–	–
$2k + \frac{2k(k+1)}{n-k-1}$	4.67	2.33	–	–
$k \log n$	6.59	4.39	–	–
Weighted SSR	4.98	6.13	4.99	19.81
AIC	10.98	10.13	10.99	23.81
AICc	9.64	8.46	9.66	22.14
BIC	11.57	10.52	11.58	24.20

<sup>a</sup>For each of the criteria (weighted sum of squared residuals (SSR), Akaike information criteria (AIC and AICc), and Schwarz criterion (BIC), the more favorable values are shown in red.

## Parameter Estimations

- Regression (minimum of the function)
- Estimators (distance measure)
- Maximum likelihood estimation (Gaussian noise)
- Identifiability (landscape in parameter space)
- Bootstrapping (sampling and noisy data)
- Cross Validation (model fitting and prediction)
- Bayesian Parameter Estimation (parameter not fixed, random variables)
- Local and Global Optimization
- Genetic Algorithms (simulations)

(Mathematica / Matlab / Systems Biology Markup Language, SBML)

## Networks

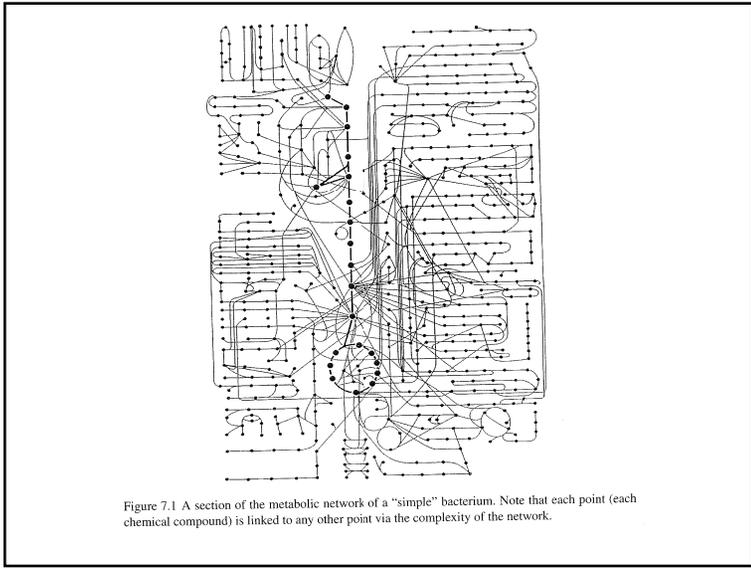
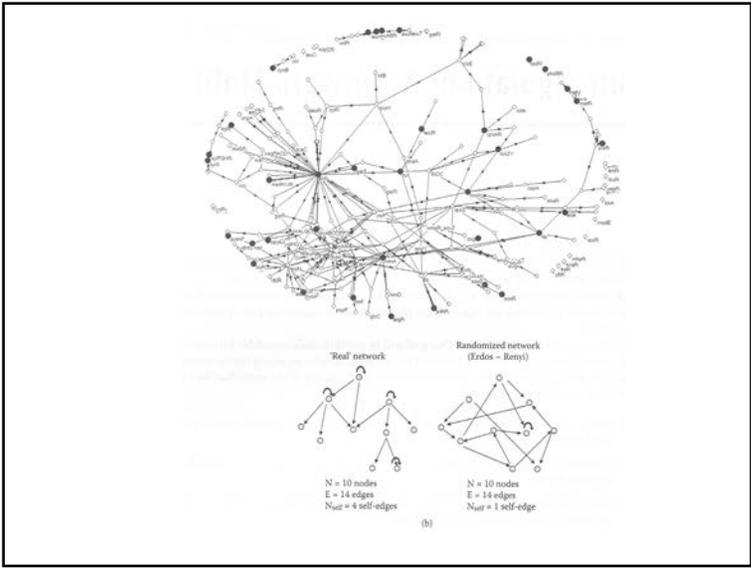
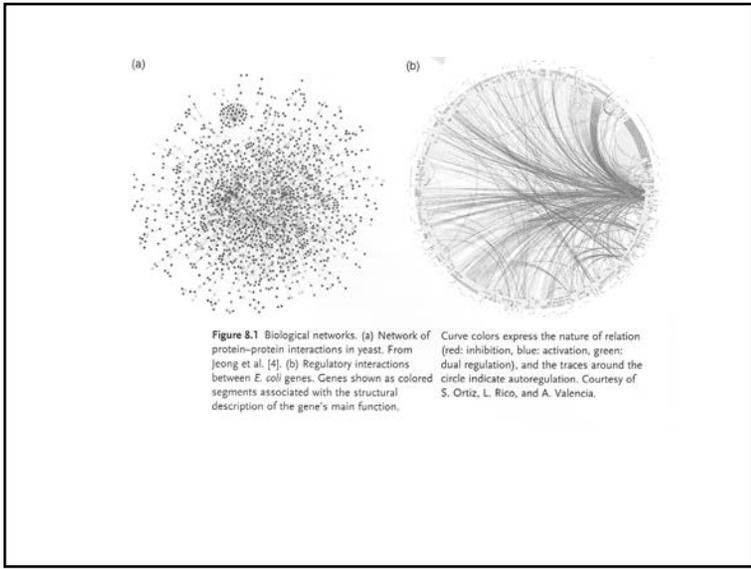
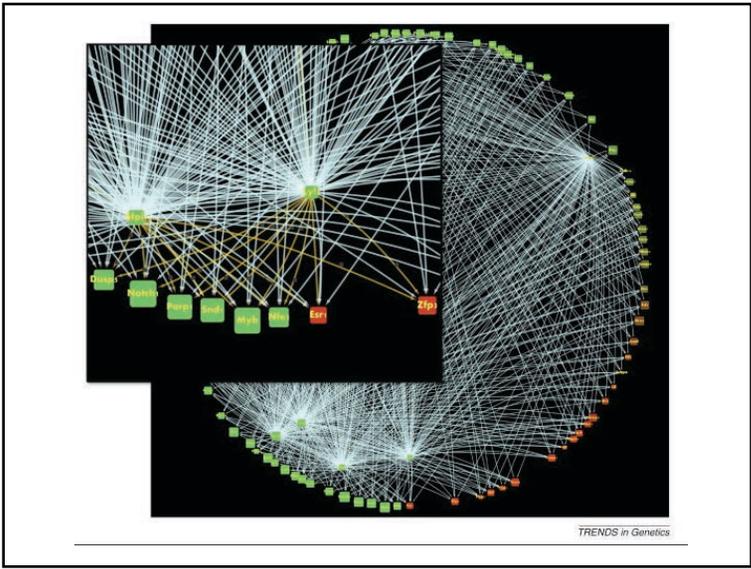
- Modules
- Nodes
- Clusters
- Interactomes

### 3.1

#### Structure of Biochemical Networks

##### Summary

The structure of complex biochemical systems – e.g., metabolism or transcriptional regulation – can be represented by networks. Nodes typically correspond to molecule types or genes, while edges represent, for instance, molecular interactions, causal influences, or correlations in high-throughput data. To detect significant structures that deserve further explanation, networks can be compared to random graphs with defined statistical properties. Various characteristic structures have been found in biological networks, including scale-free degree distributions, small average path lengths, modules and clustering, as well as network motifs.



Summary Points

1. Feedback is an essential part of molecular networks. It allows the cell to adjust the repertoire of functional proteins to current needs.
2. A FL is primarily characterized by its sign: negative feedback for maintaining homeostasis, positive feedback for obtaining ultrasensitivity or multiple stable states of the cellular composition.
3. Negative feedback can cause oscillations if signal propagation around the FL is sufficiently slow. High Hill coefficients, additional positive FLs, or saturated degradation facilitates oscillations in a negative FL.
4. Positive feedback can come from strong self-activation of a gene, from mutual repression between proteins, or by autocatalytic processes. In all cases one can obtain bistability if reactions involve some sort of cooperativity.
5. Metabolism of small molecules is characterized by a separation of scales. Typically, the intracellular pool of available small molecules is much smaller than the total amount of small molecules consumed during one cell generation.
6. Combinations of FLs in small-molecule uptake and metabolism can result in new behavioral features that are significantly different from a simple sum of the behaviors of single loops.

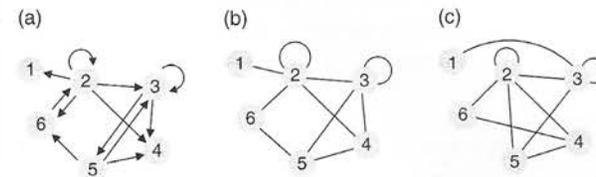
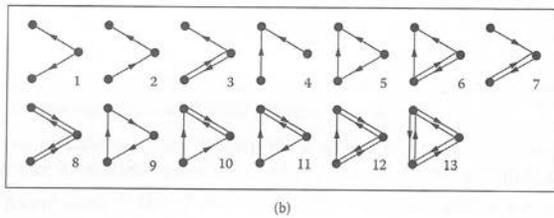
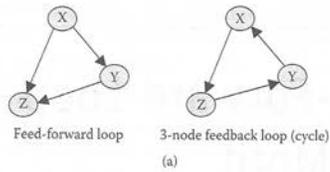
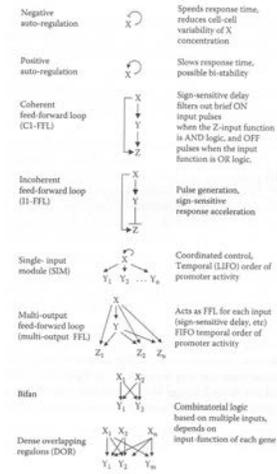
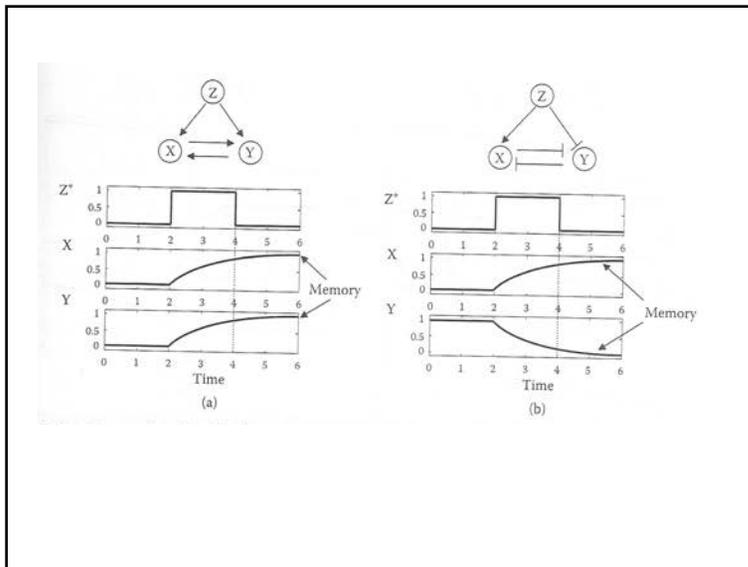
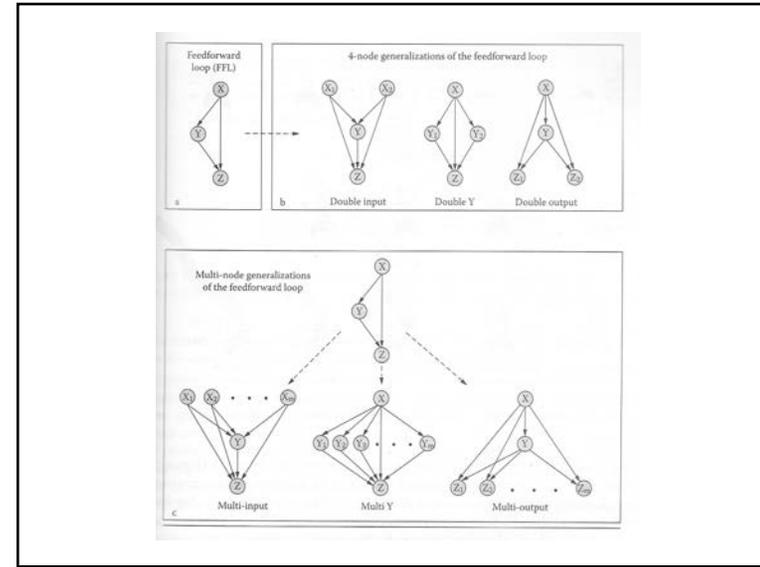
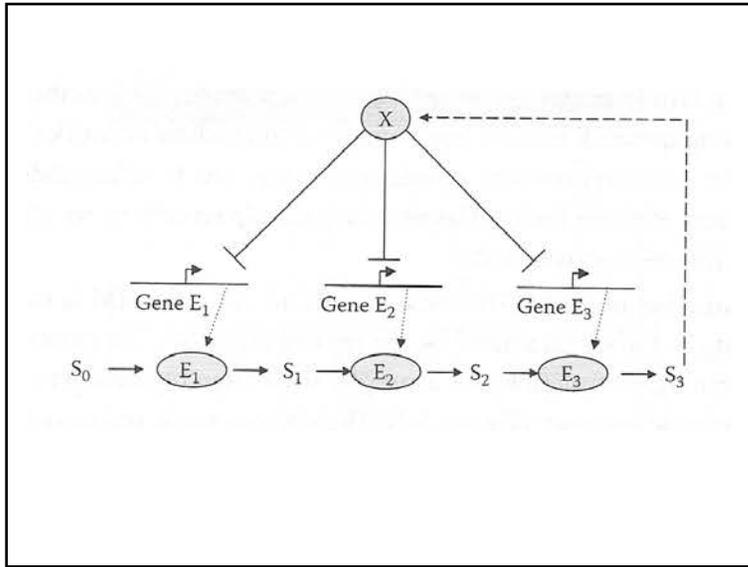
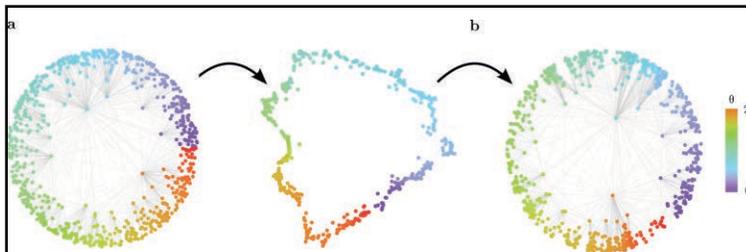
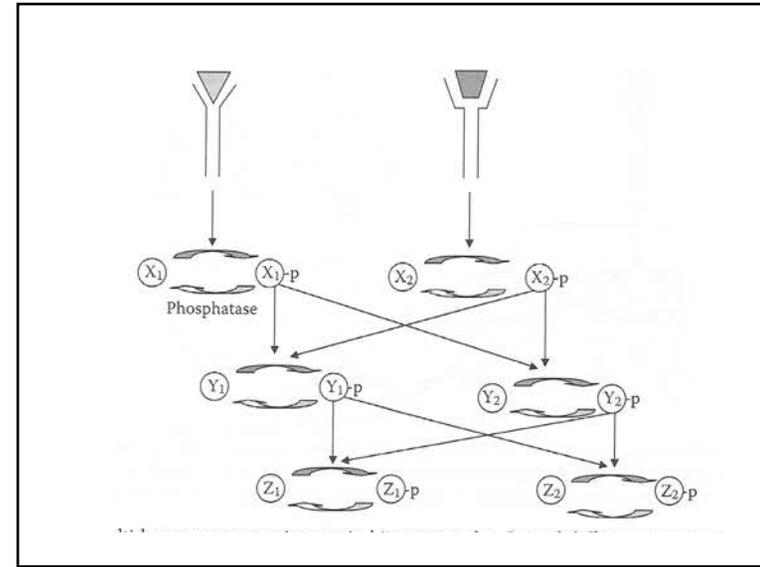
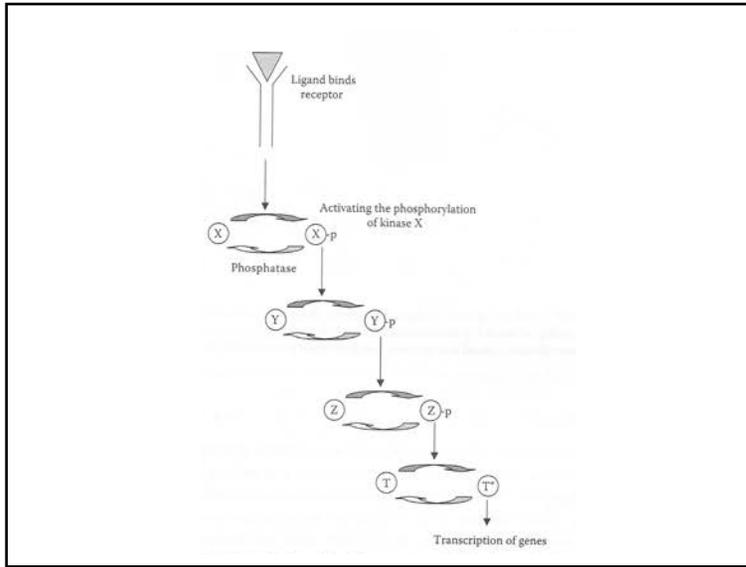


Figure 8.2 Small graphs. (a) Directed graph with 6 nodes and 9 edges. (b) An undirected graph with similar topology. (c) By rewiring, we can obtain a new graph without changing the degrees  $k_i$ .



#### Summary Points

1. Feedback is an essential part of molecular networks. It allows the cell to adjust the repertoire of functional proteins to current needs.
2. A FL is primarily characterized by its sign: negative feedback for maintaining homeostasis, positive feedback for obtaining ultrasensitivity or multiple stable states of the cellular composition.
3. Negative feedback can cause oscillations if signal propagation around the FL is sufficiently slow. High Hill coefficients, additional positive FLs, or saturated degradation facilitates oscillations in a negative FL.
4. Positive feedback can come from strong self-activation of a gene, from mutual repression between proteins, or by autocatalytic processes. In all cases one can obtain bistability if reactions involve some sort of cooperativity.
5. Metabolism of small molecules is characterized by a separation of scales. Typically, the intracellular pool of available small molecules is much smaller than the total amount of small molecules consumed during one cell generation.
6. Combinations of FLs in small-molecule uptake and metabolism can result in new behavioral features that are significantly different from a simple sum of the behaviors of single loops.



(a) A network of 750 nodes was generated by means of the PS model, with target average node degree  $2m = 10$ , scaling exponent  $\gamma = 2.75$  and network temperature  $T = 0$ . The network is embedded to the hyperbolic plane  $\mathbb{H}^2$ . An external file that holds a picture, illustration, etc. Object name is srep30108-m31.jpg with LaBNE to reveal the angular position of the nodes in the hyperbolic circle containing the network. (b) Finally, the radial coordinates of the nodes are assigned, so that they resemble the rank of each node according to its degree. By the colour of the nodes, which highlights their angular coordinates, one can note that the embedding by LaBNE is rotated by some degrees with respect to the actual node angular coordinates obtained with the PS model. This does not impact the hyperbolic, distance-dependent connection probabilities, because distances are invariant under rotations. Edges in the raw embedding by LaBNE are not shown for clarity.

**Input:**  $A$ , the  $N \times N$  adjacency matrix representing network  $G = (V, E)$   
**Output:**  $Y_{\mathbb{H}^2}$ , the hyperbolic coordinates for the set of nodes  $V$

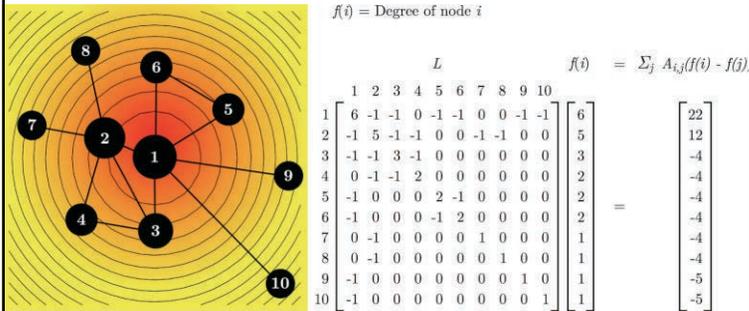
Compute the average node degree of the network  $2m$   
 Determine the network's scaling exponent  $\gamma$   
 $\beta \leftarrow 1/(\gamma - 1)$   

$$R \leftarrow 2 \ln(N) - 2 \ln \left[ \frac{2(1 - e^{-\ln(N)(1-\beta)})}{\pi m(1-\beta)} \right]$$
  
 Compute the degree matrix  $D$   
 $L \leftarrow D - A$   
 Embed  $G$  to  $\mathbb{H}^2$  via  $Lv_{k+1} \approx \lambda_{k+1} Dv_{k+1}$  with  $k = 2$   
 Since the smallest eigenvalue is 0,  $Y_{emb} = [y_1 = v_2, y_2 = v_3]$   
 Sort nodes decreasingly by degree and label them  $i = \{1, 2, \dots, N\}$   
 Assign each node with radial coordinates  $r(i) = 2\beta \ln(i) + 2(1 - \beta) \ln(N)$   
 $\theta \leftarrow \arctan(y_2/y_1)$   
 Finally,  $Y_{\mathbb{H}^2} \leftarrow [r, \theta]$

Note that to embed a network  $G$  to  $\mathbb{H}^2$ , the truncated spectral decomposition of  $L$  is used. This gives the closest approximation to the eigen-decomposition by a matrix  $\lambda_{k+1}$  of rank  $\lambda_{k+1}$  and ensures that the computational complexity of LaBNE is  $O(N^2)$ .

**Efficient embedding of complex networks to hyperbolic space via their Laplacian.**

Alanis-Lobato G, Mier P, Andrade-Navarro MA.  
 Sci Rep. 2016 Jul 22;6:30108.



**Summary Points**

1. Feedback is an essential part of molecular networks. It allows the cell to adjust the repertoire of functional proteins to current needs.
2. A FL is primarily characterized by its sign: negative feedback for maintaining homeostasis, positive feedback for obtaining ultrasensitivity or multiple stable states of the cellular composition.
3. Negative feedback can cause oscillations if signal propagation around the FL is sufficiently slow. High Hill coefficients, additional positive FLs, or saturated degradation facilitates oscillations in a negative FL.
4. Positive feedback can come from strong self-activation of a gene, from mutual repression between proteins, or by autocatalytic processes. In all cases one can obtain bistability if reactions involve some sort of cooperativity.
5. Metabolism of small molecules is characterized by a separation of scales. Typically, the intracellular pool of available small molecules is much smaller than the total amount of small molecules consumed during one cell generation.
6. Combinations of FLs in small-molecule uptake and metabolism can result in new behavioral features that are significantly different from a simple sum of the behaviors of single loops.

(a) Simple system

(b) Complex system

Perturbation



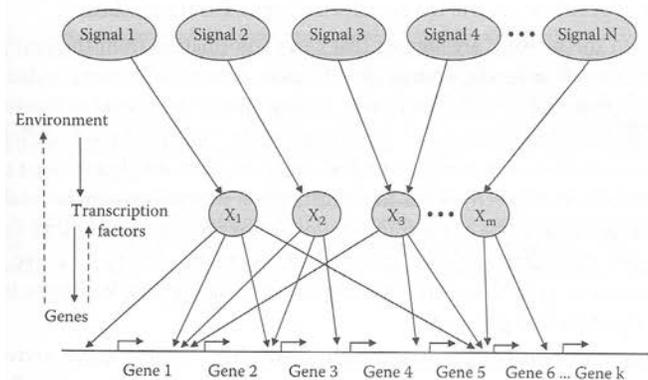
Response

Perturbation



Response

Figure 6. Response of a simple system (a) and complex system (b) to perturbation.



### 8.2

#### Network Motifs

##### Summary

Signal transduction pathways and transcription networks process biochemical signals, which are coded in the concentrations, modifications, and localization of molecules. Regulatory networks contain characteristic motifs, which may reveal small subsystems with typical dynamic behavior and specific regulatory functions. The adaptation motif, for instance, translates jumps of its input signal into a transient response, but in steady-state situations, its response is completely independent of the magnitude of the input. Other typical motifs comprise negative feedback loops, which speed up response times and contribute to stability, but also to oscillations, and the feed-forward loops, which can act as filters, sign-sensitive delays, or pulse generators.

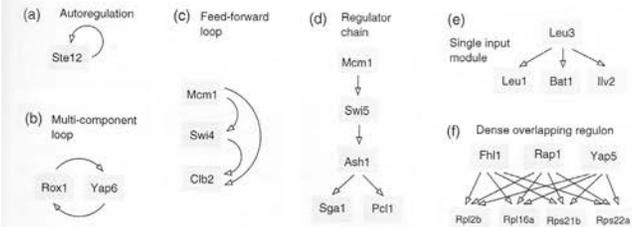


Figure 8.7 Network motifs in the transcription network of the yeast *S. cerevisiae*. Gene names refer to specific examples in the network. Redrawn from Lee *et al.* [19].

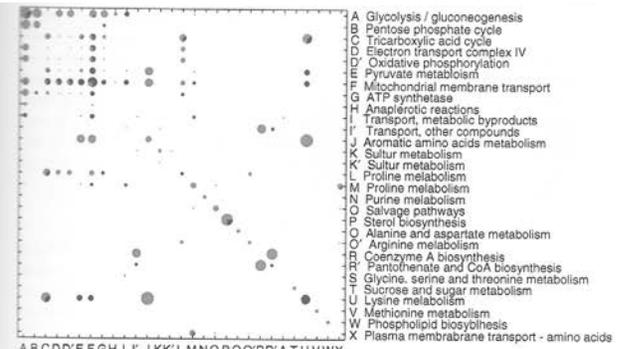
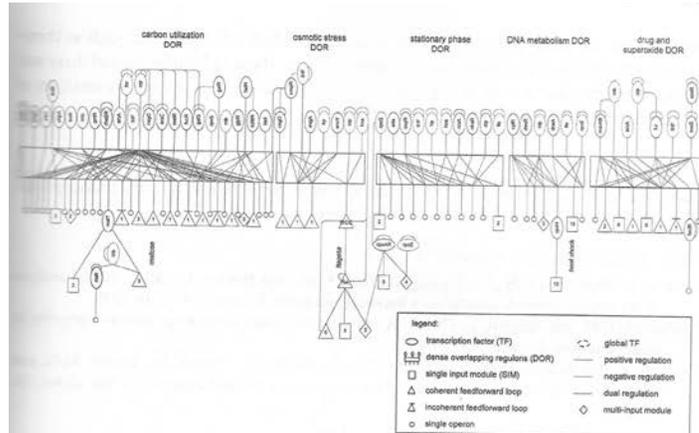
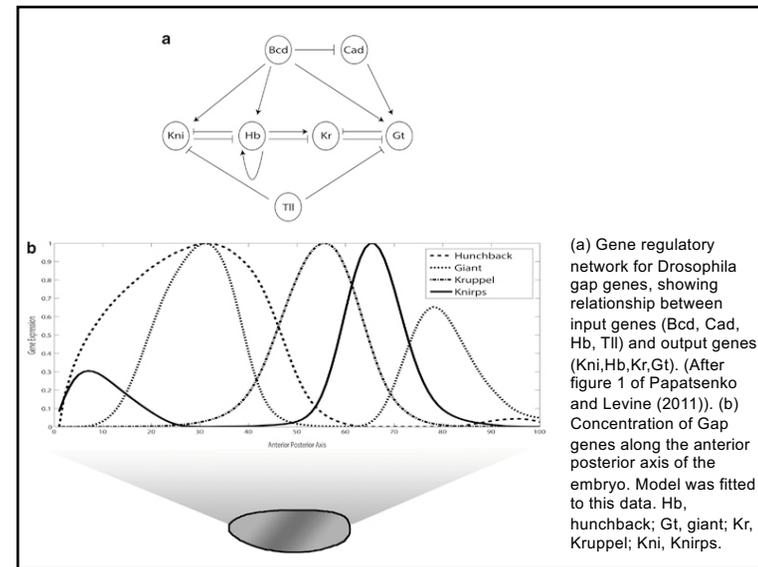


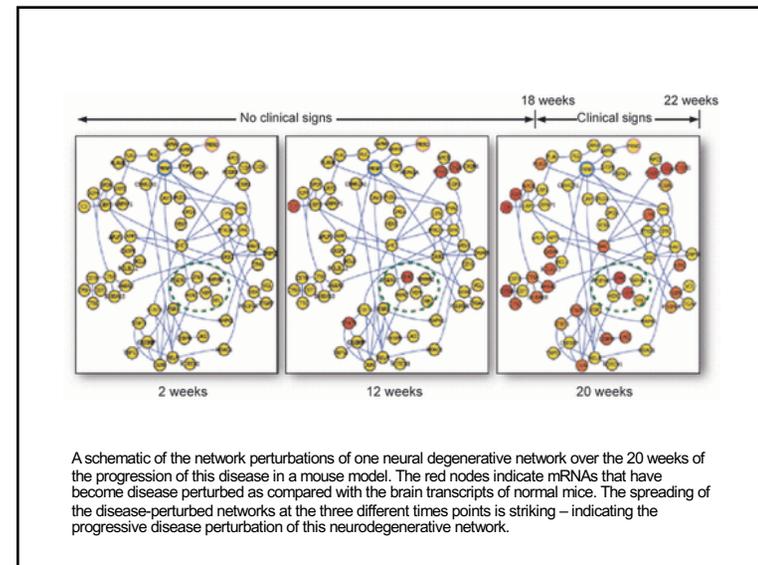
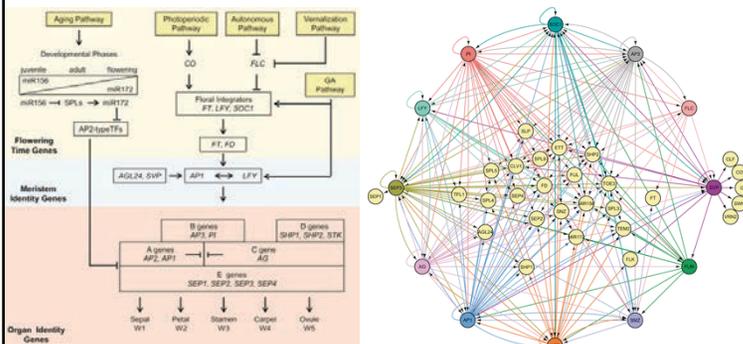
Figure 8.15 Epistatic effects reflect the shared functions of genes. Circles show the abundance of epistatic interactions between genes belonging to functional groups (rows and columns). Circle radii represent numbers of epistatic interactions. Aggravating and buffering interactions are shown as red and green pie slices, respectively. From Segre *et al.* [66].

Transcription network in bacteria

# Network Application Examples

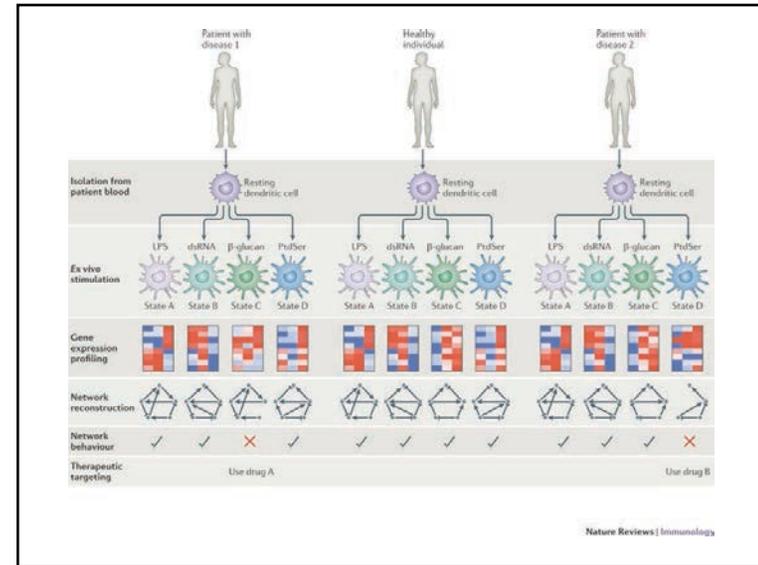
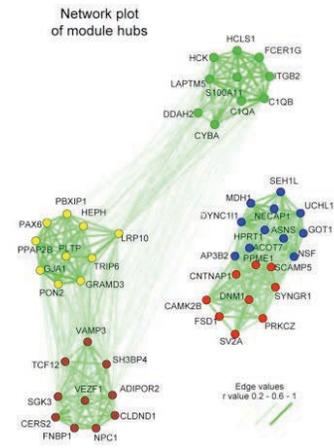


## The (r)evolution of gene regulatory networks controlling Arabidopsis plant reproduction: a two-decade history.



**Systems biology and gene networks in neurodevelopmental and neurodegenerative disorders.**

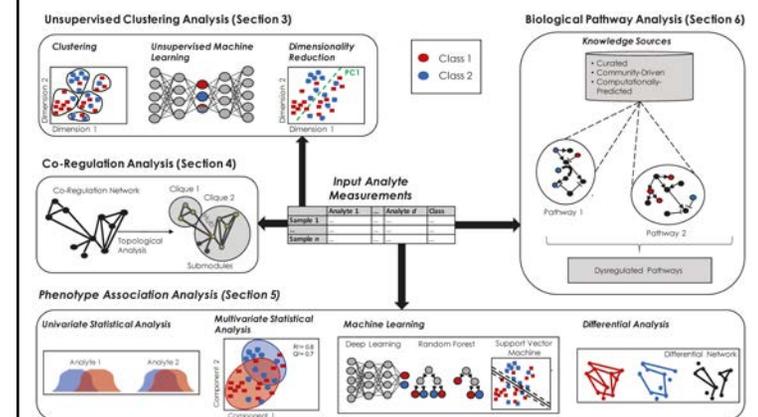
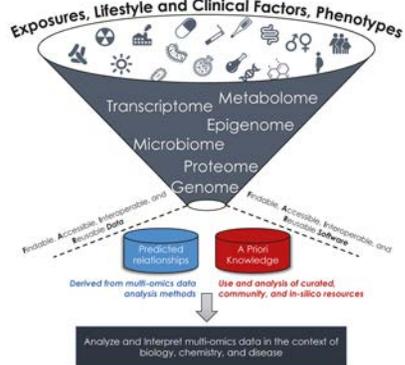
Parikshak NN, Gandal MJ, Geschwind DH. Nat Rev Genet. 2015 Aug;16(8):441-58.



**Metabolomics and Multi-Omics Integration: A Survey of Computational Methods and Resources**

Eicher T, Kinnebrew G, Patt A, Spencer K, Ying K, Ma Q, Machiraju R, Mathé AEA.

Metabolites. 2020 May 15;10(5):202.



**Table 1. Examples of multi-omics applications using unsupervised analysis.**

Type of Method	Functionality	Reference	
Dimensionality Reduction	t-Distributed Stochastic Neighbor Embedding (t-SNE)	[46]	
Clustering	Visualize prefrontal cortex metabolites and lipids by human population group.	[47] †	
	Identify multi-omic molecular subtypes in hepatocellular carcinoma.	[49] †	
	Identify multi-omic clusters in breast tumor tissue associated with prognosis.	[49] †‡	
	Identify lipid-protein-metabolic clusters associated with diabetes and periodontal disease.	[50]	
	Partitioning Around Medoids (PAM)	Identify microbial-metabolic clusters associated with diarrhea.	[51] †‡
	Gaussian Mixture Modeling (GMM)	Identify clinical depression score clusters associated with blood metabolomic and genomic data in blood to predict drug response.	[52] †
Other Machine Learning Methods	Density-Based Spatial Clustering of Applications with Noise (DBSCAN)	Evaluate the impact of bacterial metabolism on mucosal immunity.	[53]
	Random Forest	Identify clusters of histological stromal features associated with prognosis and metabolites in cancer-associated fibroblasts.	[54] †
	Autoencoder	Cluster plasma protein and metabolite levels to identify temporal trends in murine cardiac remodeling.	[55]

\* Raw data are available in the supplementary of the referenced manuscript, or a public repository. † Preprocessed data are available in the supplementary of the referenced manuscript, or a public repository. ‡ Descriptive statistics are available in a table or supplementary materials of referenced manuscript. Unmarked data are available upon request from the authors or from a consortium.

**Table 2. Examples of multi-omics applications using co-regulation analysis.**

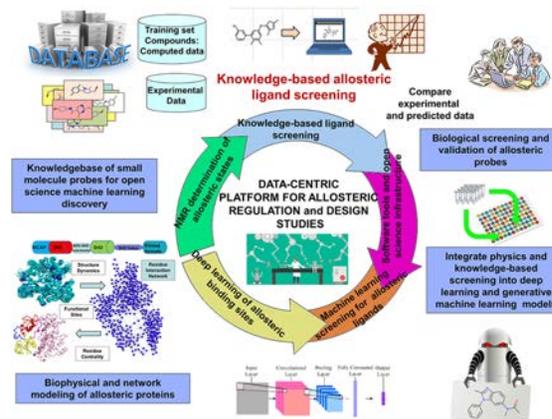
Type of Method	Functionality	Reference	
Associative Networks	Correlation Networks	Find metabolic-metabolic associations specific to or shared across blood, urine, and saliva. Find modules of blood metabolites and genes associated with body weight change. Find associations between serum, blood, and gut antibodies, metabolites, and microbiome and patient disease activity reports in inflammatory bowel disease.	[51] † [52] † [53] †‡
	Partial Correlation Networks	Find associations between metabolites, transcripts, cytokines, and self frequencies in plasma and whole blood associated with adaptive immune response to Herpes zoster vaccine. Visualize associations between sleep survey responses and levels of serum cytokines, metabolites, lipids, proteins, and genes. Visualize associations between metabolites and lipids associated with metabolic disease treatment in rat liver tissue and clinical chemistry measurements from serum.	[54] † [55] †
Topological Analysis of Networks	Weighted Gene Co-expression Network Analysis (WGCNA)	Characterize complex transcriptional and metabolic traits in major depressive disorder. Identify co-regulated modules of blood metabolites and transcripts in children with asthma.	[57] † [58] †
	Subnetworks	Identify co-regulated modules of metabolites and transcripts in glycaetoma multiforme. Identify subnetworks of correlated proteins and metabolites in adrenocorticotrophic hormone-secreting pituitary adenomas. Identify subnetworks of correlated genetic, proteomic, metabolomic, clinical, and microbiome data from multiple biobanks in cardiovascular disease.	[59] [60] [61] †

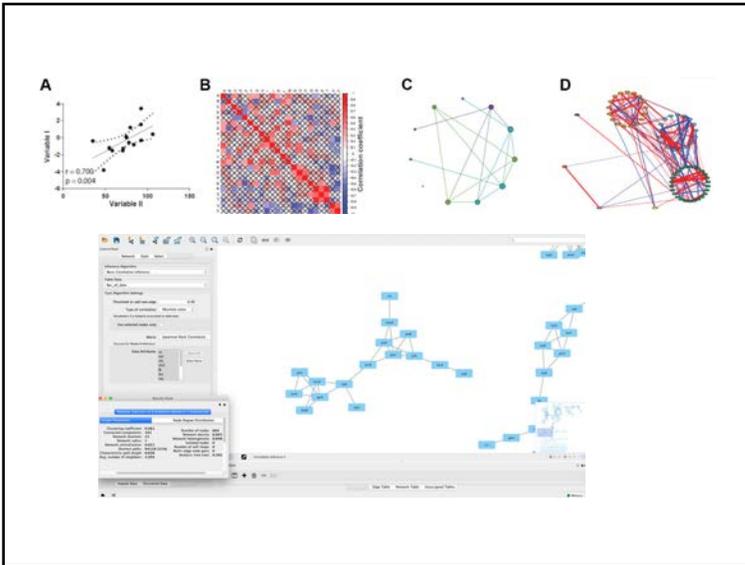
\* Raw data are available in the supplementary of the referenced manuscript, or a public repository. † Preprocessed data are available in the supplementary of the referenced manuscript, or a public repository. ‡ Descriptive statistics are available in a table or supplementary materials of referenced manuscript. Unmarked data are available upon request from the authors or from a consortium.

**Table 3. Examples of multi-omics applications that identify analytes associated with phenotype.**

Type of Method	Functionality	Reference
Univariate Statistical Methods	Student's t test and effect size	Identify metabolites, miRNAs, mRNAs, and lncRNAs altered by response to benzoylperoxide to identify mechanisms of toxicity. [62]
Multivariate Statistical Methods	Partial Least Squares Discriminant Analysis (PLS-DA) (and variants)	Identify breast tumor tissue metabolites that differentiate MDR tumors. [63]
		Identify metabolites that differentiate normal and tumor tissue in the pancreas. Identify differences between Obese/obese and control groups in gut microbes, serum metabolites, miRNAs, and cytokine levels. Diagnose temporal changes in plasma lipid and metabolite patterns from normal and hyperlipidemic patients. [64] †
Linear Models (and variants)		Identify metabolites that predict prostate cancer associated with continuous CT scan features in cyst fibrosis. [65]
		Identify serum metabolites associated with second degree heart failure from MRI and serology. [66]
Identifying Analyte Relationships that Clink by Phenotype	DMC	Identify plasma metabolites and proteins associated with prognosis in acute cholecystitis patients. [67]
	Inf-DM	Find associations between blood DNA methylator and metabolite levels in smokers. Identify differences in analytic metabolite correlations between traumatically brain injury and control groups. [68] †
Machine Learning Methods for Predicting Phenotype	Random Forest	Identify genes of fluid metabolites and blood and bone marrow transcripts that differentiate between osteoarthritis and rheumatoid arthritis. Identify serum metabolites, proteins, and lipids associated with osteoarthritis, osteoporosis, and control groups. Identify metabolites and other analytes predictive of weight gain and loss. [69] †
		Identify metabolites, serology, and proteome profiles of protein quality traits. [70] †
Support Vector Machine (SVM)		Identify metabolites and transcriptomic profiles of liver cancer in the liver. [71] †
Multiple Regression (MR)		Predict metabolic levels using genes and metabolites in liver and hepatocellular carcinoma. [72]
Convolutional Neural Networks (CNN)		Predict early and late stage Alzheimer's using urinary metabolites and genes. [73]
		Predict early onset injury using serum metabolites. [74]
Recurrent Neural Networks (RNN)		Integrate transcriptomic and metabolite levels to predict cellular state in Escherichia coli. [75] †

\* Raw data are available in the supplementary of the referenced manuscript, or a public repository. † Preprocessed data are available in the supplementary of the referenced manuscript, or a public repository. ‡ Descriptive statistics are available in a table or supplementary materials of referenced manuscript. Unmarked data are available upon request from the authors or from a consortium.

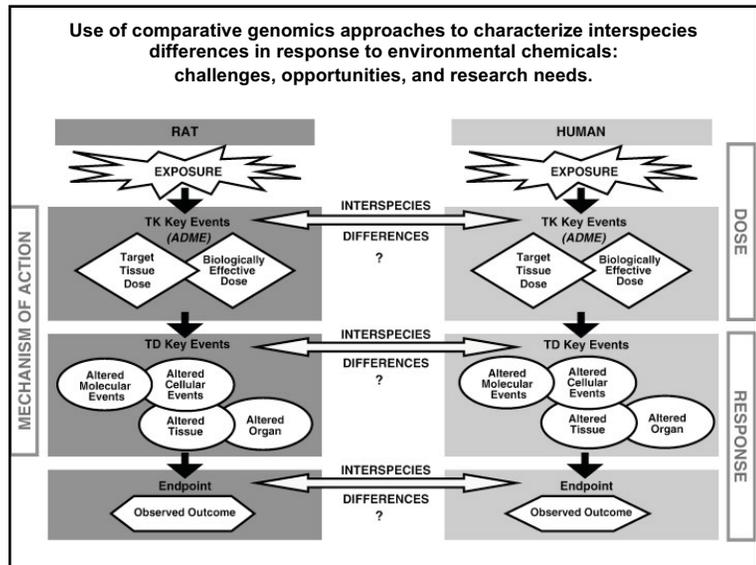
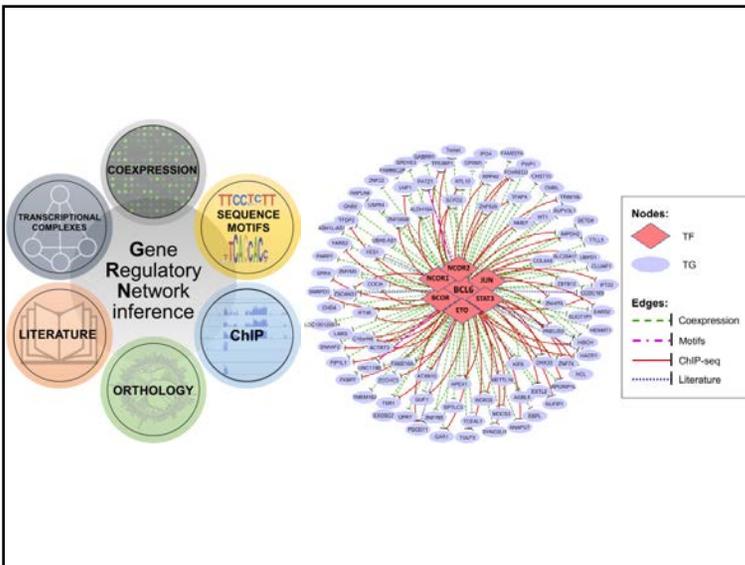


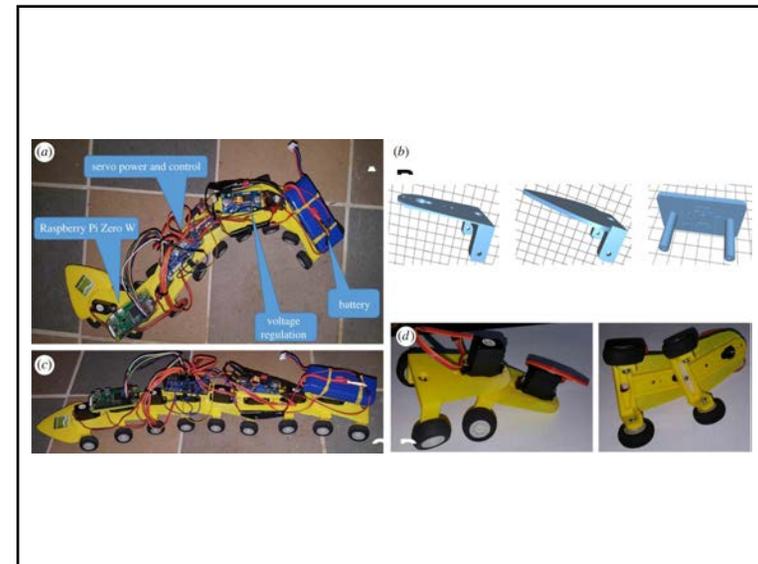
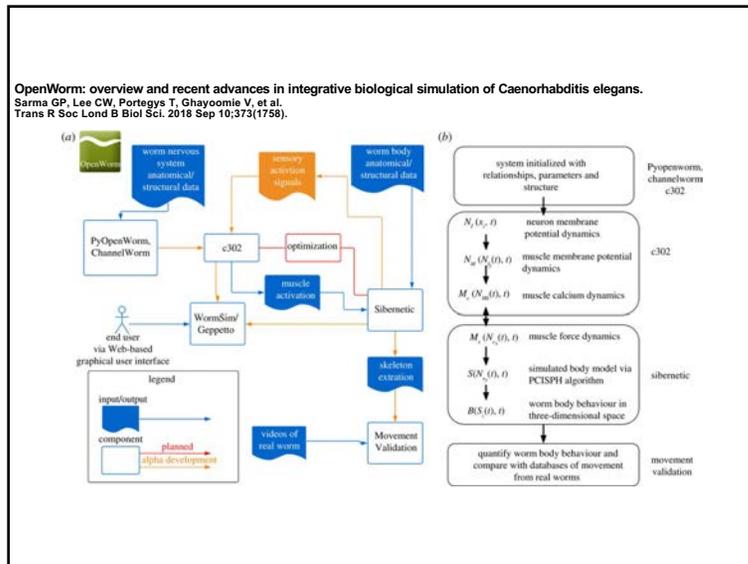
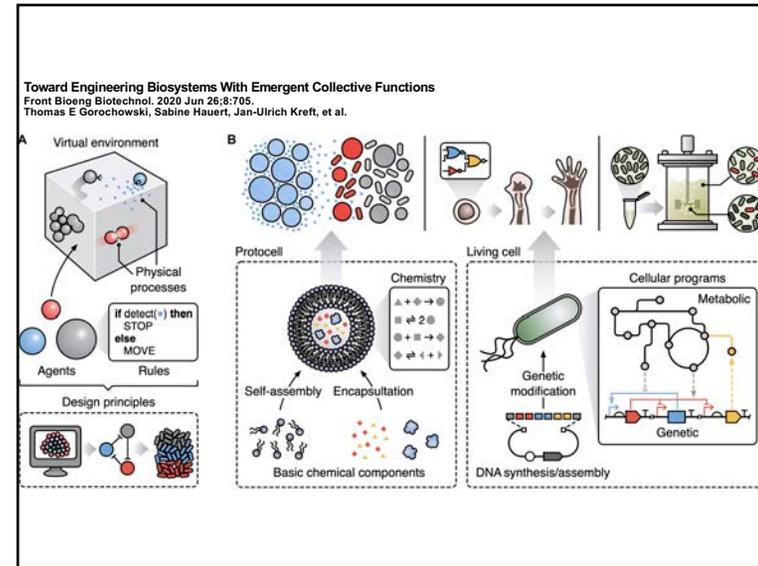
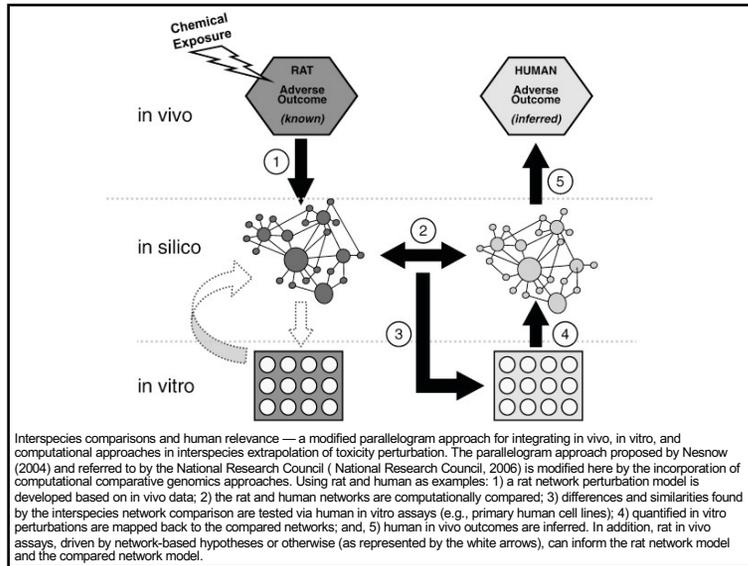


**Leveraging User-Friendly Network Approaches to Extract Knowledge From High-Throughput Omics Datasets**  
 Pablo Ivan Pereira Ramos, Luis William Pacheco Arge, Nicholas Costa Barroso Lima, Kiyoshi F Fukutani, Artur Trancoso L de Queiroz  
 Front Genet. 2019 Nov 13;10:1120.

Tool	Description	Category	Reference/URL
Biogenet	Retrieves interactions associated with input IDs. Sophisticated UI gives links to GO, KEGG, etc.	Interaction database	Martin et al., 2010
CyBioSVM	Developed for identification of cancer biomarkers using machine learning approaches.	PPI-network	Shi et al., 2017
CyPath2	Pathway Commons (BioPAX L3 database) web service graphical user interface client app.	Interaction database	<a href="http://apps.cytoscape.org/apps/cyath2">http://apps.cytoscape.org/apps/cyath2</a>
CytoGEDEVO	Pairwise global alignment of PPI or other networks.	PPI-network	Musik et al., 2016
CytoMOBAS	Identifies and analyses disease associated and highly connected subnetworks.	Disease-disease association PPI-network	<a href="https://apps.cytoscape.org/apps/cytomobas">https://apps.cytoscape.org/apps/cytomobas</a>
DeDai	Applies data dimensionality reduction methods for designing insightful network visualizations.	PPI-network	Czerwinski et al., 2015
INTERSPA	Free online resource for protein interaction comparison between species.	Not a Cytoscape app	Kwon et al., 2018
NetworkAnalyst	Free online resource for network construction and analysis.	Not a Cytoscape app	Zhou et al., 2019
PathLinker	Reconstructs the interactions in a signaling pathway of interest from the receptors and TFs in a pathway, and can be broadly used to compute and analyze a network of protein interactions.	PPI-network	Gi et al., 2017
PiMeasure	Compute link weights and assess the reliability of the links in a network including PPI.	PPI-network	Zaki et al., 2013
PEPPER	Find meaningful pathways / complexes connecting a protein set members within a PPI network using multi-objective optimization.	Functional module detection	Winterhalter et al., 2014
PINA	Free online resource capable of PIN construction, filtering, analysis, visualization and management.	Not a Cytoscape app	Wu et al., 2009; Cowley et al., 2012;
PINORA	Protein interaction network-based Pathway Analysis.	Random walk with restart algorithm	Hwang et al., 2015
PSIOQC	PSIOQC Web Service Client for importing interactions from public databases.	Interaction database	Aranda et al., 2011
Universal Client stringApp	Import and augment Cytoscape networks from STRING.	Gene-disease association; PPI-network	Doncheva et al., 2019

PINA, protein interaction network analysis; INTERSPA, inter-species protein interaction analysis; PINORA, protein interaction network-based pathway analysis.





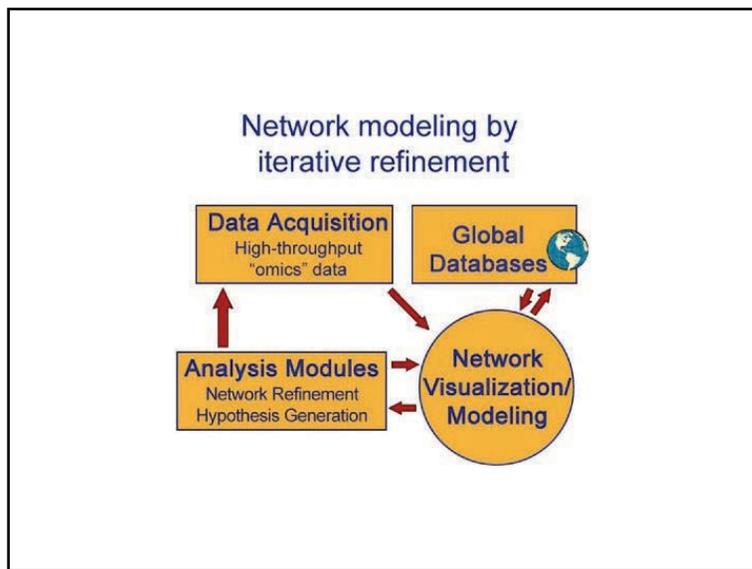
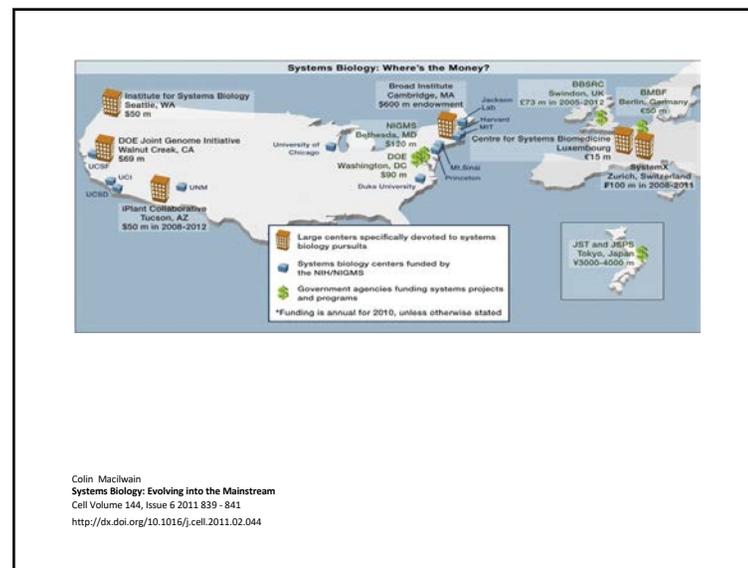
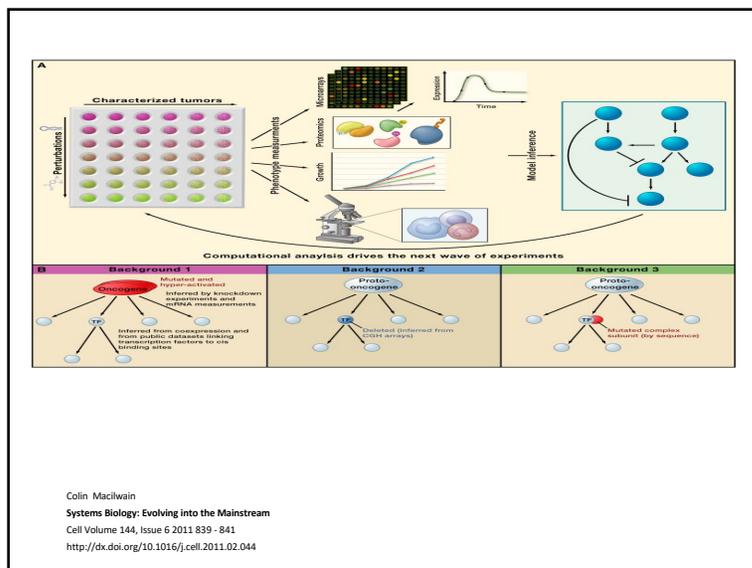


Table 1. Summary of the datasets used in systems biology based drug design paradigm and the nature of the hypothesis that can be inferred from these analyses.

Data type	Parts list	Hypothesis from a retrospective analysis of the interactions
Cheminformatics	<u>Nodes:</u> Chemicals <u>Node Attributes:</u> Protein, Domains, Substructures, Enriched fragments, Pharmacophores, Toxicophores, Physicochemical properties, Structural descriptors, etc	(a) Chemical similarity network analysis that can complement chemoproteomic and chemogenomic analysis.
Proteomics	<u>Nodes:</u> Proteins <u>Node Attributes:</u> Domain definitions, Sequence motif/linear and non-linear, Superfamily definitions, Sequence descriptors, Cysteine ligands, Pathways, other protein interacting partners	(a) Protein similarity and (b) protein interaction networks
Genomics	<u>Nodes:</u> Genes/ transcripts <u>Node Attributes:</u> Phenotypes/indications, Promoters/genes/ small molecule or siRNA(s), growth regulators, TFs, Epigenetic factors, Master regulators, Pathways, Literature gene sets	(a) Finding and interpreting genes/transcripts associated with phenotypic changes or perturbations.
Phenomics	<u>Nodes:</u> Diseases/ indications/ phenotypes <u>Node Attributes:</u> in vivo Biochemical data, Hematology, Organ Weight, Pathology Data, Histology, Pathways, Genes, Proteins (drug targets), Chemicals, Chromatin regulators.	(a) Studying the genotype-phenotype map, (b) Identifying the genetic basis of complex traits.
Chemoproteomics (bipartite networks - edges between chemicals and proteins only)	<u>Nodes:</u> Chemicals, Proteins <u>Edge Attributes:</u> Activation, inhibition, degradation.	(a) Analyzing the pharmacological map of the druggable proteome and discovering ligands for undruggable proteome, (b) drug target discovery.
Chemogenomics (bipartite networks - edges between chemicals and genes only)	<u>Nodes:</u> Chemicals, Genes <u>Node Attributes:</u> in vivo Biochemical data, Hematology, Organ Weight, Pathology Data, Histology, Pathways, Genes, Proteins (drug targets), Chemicals, Chromatin regulators. <u>Edge attributes:</u> activation, repression.	(a) Determining mode of action, (b) drug repurposing and drug target identification
Qualitative and quantitative network models	<u>Nodes:</u> Chemicals, Genes, Proteins, protein complexes, phenotypes <u>Node Attributes:</u> Activity levels inferred from mRNA or protein expression activity data. <u>Edge Attributes:</u> Regulatory interactions, PTMs.	(a) Represent existing knowledge of biological systems, (b) predict the effect of perturbations on other components of the pathway, (c) identify missing components in a pathway, (d) determine the most critical components of the pathway.



**“Epigenetics and Systems Biology”**

**Spring 2021 (Odd Years)**

**Biol 476/576**

**Schedule/Lecture Outline**

Week 1	(Lesson 1)	Systems Biology (History/ Definitions/ Theory)
Week 2	(Lesson 2)	Systems Biology (Networks & Emergence)
Week 3	(Lesson 3)	Systems Biology (Components: DNA to Phenotype)
Week 4	(Lesson 4)	Systems Biology (Genomics / Technology)
Week 5	(Lesson 5)	Epigenetics (History / Molecular Processes)
Week 6	(Lesson 6)	Epigenetics (Molecular Processes & Integration)
Week 7	(Lesson 7)	Epigenetics (Genomics and Technology)
Week 8	(Lesson 8)	Cell & Developmental Biology
Week 9	(Lesson 9)	Epigenetics of Cell & Developmental Biology
Week 10	(Lesson 10)	Environmental Impact on Biology
Week 11	(Lesson 11)	Environmental Epigenetics
Week 12	(Lesson 12)	Disease Etiology
Week 13	(Lesson 13)	Epigenetics & Disease Etiology
Week 14	(Lesson 14)	Evolutionary Biology & Genetics
Week 15	(Lesson 15)	Epigenetics & Evolutionary Biology
Week 16	(Lesson 16)	Grant Review/ Study Section Meeting