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


Background Book References


Literature


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

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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/thenones, 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

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http://www.ajpcell.org
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 2δ (Camk2d) and protein kinase B-α (Akt1). In fact, the top ranked protein kinase in the Bayes’ analysis, calcium/calmodulin-dependent protein kinase 2δ, 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).

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REFERENCES

Original research

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

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A B S T R A C T

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.

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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.1

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

1 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).
subjective 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 Aristotle2), 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 autopoesis, the more recent Developmental Systems Theory or DST, as in Oyama, 1985/2000, or DST, as in Oyama, 1985/2000) and genetic reductionism (as put forth in Varela and his partisans (Weber 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” (Ruíz-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 ‘ontophylogensis’ (a term somewhat reminiscent of Buss, 1987, who also felt that evolutionary accounts of phylogensis needed to be supplemented with accounts of ontogenesis, the emergence of the individual; 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 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).

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 privilege 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:

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

3 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 metaphysical form — 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.

4 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 determination. 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 (clinem) — 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 discovery 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).5

There are no essences here, no Platonic forms or first principles like Aristotle’s nous (‘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 nous 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 evolutionist defy 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 disembodiment 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 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 conflation 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 processedualized; 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 inheritability 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 substantalist view, that organisms are something special — norganisms, in Julian Huxley’s ironic phrase describing Haldane’s reaction to his own mechanist views6 — 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...
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 Tyndall7 and onto Dennett and Kupiec, the type of biological theory that asserts the primacy of change 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” (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 seems to find a ‘third way’ between the two:

Ontophylogeny 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 ontophylogeny, as its name indicates, fuses ontogenesis (the production of the individual) and phylogeny (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 Modem 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 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 organicist 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 camouflage 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 ontogeny hypothesis, 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-jeopardic sense in which this term also applies to Claude Bernard, who after all is something of a father figure in the analysis of ontogeny). 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-organicist 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:

[What 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, 1863/1927, 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 finalism 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 adrenaline secretion will affect the concentration of sugar in the blood” (Levins and Lewontin, 1980, p. 72). “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” programed by our genes (Dawkins, 1976, p. 21; useful discussion in Godfrey-Smith, 2001). Kupiec’s reappraisal 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); it has more creativity attached and, perhaps,
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.

Ultimately, as Oyama also does today.

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 organismist theory) and the faith in the absolute explanatory power of componential analysis (as found always in reductionism).

Acknowledgements

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

References


9 I thank both reviewers for remarks leading me to see this point.
Systems biology: current status and challenges

Anze Zupanic¹ · Hans C. Bernstein²,³ · Ines Heiland⁴

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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...
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—isgsb.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


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Course Title: Epigenetics and Systems Biology

Course Description:
Epigenetics and Systems Biology (Biol 474/576) is an interdisciplinary course that explores the role of epigenetics in the regulation of gene expression and the development of complex diseases. The course covers topics such as DNA methylation, histone modifications, microRNAs, and their role in disease progression. Students will learn about the epigenetic mechanisms and their impact on cellular function and disease development.

Course Structure:
The course consists of lectures, discussions, and lab sessions. It is divided into two main parts: (1) Epigenetics and (2) Systems Biology. Each part is further divided into several modules, covering various aspects of epigenetics and systems biology.

Course Requirements:
- **Credit Hours:** 3
- **Meeting Times:** Tuesdays and Thursdays, 2-3 PM
- **Location:** Biological Sciences Building, Room 101

Course Syllabus:
- **Lecturer:** Prof. John Doe
- **TAs:** Jane Smith, Mike Johnson

Course Schedule:
- **Week 1:** Introduction to Epigenetics
  - Topics: Basics of DNA Methylation and Histone Modifications
  - Readings: Chapters 1-2 from the textbook
- **Week 2:** DNA Methylation
  - Topics: DNA methylation and its role in gene regulation
  - Readings: Chapters 3-4 from the textbook
- **Week 3:** Histone Modifications
  - Topics: Histone modifications and their role in gene regulation
  - Readings: Chapters 5-6 from the textbook
- **Week 4:** MicroRNAs
  - Topics: MicroRNAs and their role in gene regulation
  - Readings: Chapters 7-8 from the textbook
- **Week 5:** Epigenetic Diseases
  - Topics: Epigenetic changes in various diseases
  - Readings: Chapters 9-10 from the textbook

Grading:
- **Exams:** 30%
- **Assignments:** 40%
- **Project:** 30%

Textbook:
- *Epigenetics and Systems Biology* by Jane Doe

Course Policies:
- **Late Policy:** No late assignments will be accepted.
- **Missed Exams:** Must be made up within 1 week of the exam date.
- **Tutoring:** Free tutoring available through the university's tutoring center.

Important Dates:
- **First Day of Classes:** September 1, 2023
- **Last Day to Drop:** October 1, 2023
- **Final Exam:** December 15, 2023, 10 AM-12 PM

Additional Information:
- **Office Hours:** Tuesdays, 3-4 PM
- **Email:** john.doe@university.edu

Welcome to the course! If you have any questions, feel free to contact me.
Spring 2021: Epigenetics and Systems Biology
Lectures Online – Systems Biology
Michael K. Skinner – Biol 476/576
11:00-11:50 am, Tuesdays & Thursdays
January, 2021
Weeks 1 and 2

System Biology
• History and Definitions
• Reductionist/Genetic Determination
• Holistic Emergentism/ Homesostasis or Robustness
• Revolutionary and Evolutionary Systems Biology
• Networks and Computational Biology
• Basic Molecular and Cellular Components

Required Reading
131–23.


Background Book References
David Andelman (2012) A First Course in Systems Biology, Garland Science

Systems Biology

Discussion
Student 1: Ref #1 above
-What is 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

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).

History

Theory

Paradigm Shift

Parameters

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 equalibrium and homeostasis
  -Discovery DNA/Structure/Genes (Molecular Biology)
  -Computational Biology (non-equalibrium thermodynamics and kinetics metabolism)
2000s -Genome Sequence
  -Oomics Technology

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 $\rightarrow$ Anomaly
(b) Anomaly $\rightarrow$ Crisis
(c) Crisis $\rightarrow$ Extraordinary science
(d) Extraordinary science $\rightarrow$ 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 dis equilibrium 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 Biotic (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 (Omic technologies)

**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**

<table>
<thead>
<tr>
<th>Revolutionary systems biology</th>
<th>Evolutionary systems biology</th>
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<tbody>
<tr>
<td>1. Holism</td>
<td>Reducationism</td>
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<td>2. Top-down causation</td>
<td>Bottom-up causation</td>
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<td>3. Epigenetics</td>
<td>Genetic determinism</td>
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<td>4. Emergentism</td>
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<td>5. Synergism</td>
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<td>6. Robustness</td>
<td>Homeostasis</td>
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<tr>
<td>7. Nonlinear dynamics</td>
<td>Linear stasis</td>
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</table>
Neuropharmacology beyond reductionism - A likely prospect.
Margineanu DG.

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, and the understanding of 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 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 overly 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.

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

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 overly 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.

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 mathematically-physical-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 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.

"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

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.
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 (輪廻 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.
Hierarchy, determinism, and specificity in theories of development and evolution

Uwe Deichmann

Published online: 30 October 2017
© Springer International Publishing AG 2017

Abstract The concepts of hierarchic organization, genetic determinism and biological specificity (the 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 and 1950s with genetic molecules, viruses and proteins as major objects of research often labeled “reductionist”. However, the concepts have been marginalized or repeated since the research that in the late 1980s began to focus additionally on the molecularization of complex biological systems and functions using systems approaches. This paper challenges the view that “molecular reductionism” has been accurately replaced by holistic and a focus on the collective behavior of cellular entities. It argues instead that there are more viable explanations for “molecular reductionism”, in which genetics, embryology, biochemistry, and computer science interweave and result in research that is an exact and causally precise as earlier molecular biology.

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

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

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<tr>
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Two applications of network-based analyses of GWAS. (a) GWAS analysis computes the association between a SNP and case/control, reporting a P-value for each SNP. (b) Causal gene identification is the problem of identifying a single causal gene (circled in red) for the phenotype from a larger locus of candidate genes that is significantly associated with the phenotype. (c) Causal network identification is the problem of finding a group of interacting genes (e.g. a signaling pathway or protein complex) containing SNPs that distinguish cases and controls.
Weight Stigma Reduction and Genetic Determinism.
Hilbert A.

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 = 126) 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-Aylon M.

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 emphasize 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 'assemblage' 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 bioculturalism - 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.
Epigenetics

Waddington (1940s) coined term to describe environment-gene interactions that promote phenotype.

Non-genetic factors in the control of developmental processes and phenotype (? anti-genetic determinism)

Art Riggs (1996), defined as "mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence"

Epigenetics represents for many systems biologists a promise for control of biological phenomena unfulfilled by genetic determinism (Silverman 2004)

Epigenetic Mechanisms of Gene Regulation

- DNA Methylation
- Histone Modification
- Chromatin Structure
- DNA Organization into Domains (eg Loops)
- Nuclear Compartmentalization (eg nuclear matrix)
- Noncoding functional RNAs

Epigenetics

Molecular factors/processes around the DNA that regulate genome activity, independent of DNA sequence, and are mitotically stable
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 intitials 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.**

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

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"

Migliani (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.
Illustration of redundancy (A) and distributed robustness (B). Plots show a hypothetical organization in which an upstream signal from the upper white circles is processed by a number of intermediate components (dark circles) to a downstream effector (lower white circles).

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

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Table 1. Categorizations of systems biology

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<thead>
<tr>
<th>Type One</th>
<th>Type Two</th>
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"Epigenetics and Systems Biology"
Spring 2021 (Odd Years)
Biol 476/576

Schedule/Lecture Outline

<table>
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<tr>
<th>Week</th>
<th>(Lesson)</th>
<th>Systems Biology (History/ Definitions/ Theory)</th>
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<tr>
<td>1</td>
<td>(Lesson 1)</td>
<td>Systems Biology (Networks &amp; Emergence)</td>
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<td>2</td>
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<td>Systems Biology (Components: DNA to Phenotype)</td>
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<td>3</td>
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<td>Systems Biology (Genomics, Technology)</td>
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<td>4</td>
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<td>Epigenetics (History, Molecular Processes &amp; Integration)</td>
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<td>5</td>
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<td>Cell &amp; Developmental Biology</td>
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<td>Epigenetics &amp; Disease Evolution</td>
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<td>11</td>
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<td>Evolutionary Biology &amp; Genetics</td>
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<td>12</td>
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<td>Epigenetics &amp; Evolutionary Biology</td>
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<td>13</td>
<td>(Lesson 13)</td>
<td>Grant Review/ Study Session Meeting</td>
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Top-down models in biology: explanation and control of complex living systems above the molecular level.
Spring 2023 – Epigenetics and Systems Biology
Lecture Outline – Systems Biology
Michael S. Shinu – Med 474/C746
10:30 a.m., Tuesdays & Thursdays
Weeks 1 and 2

Systems Biology:
• History and Definitions
• Reductionism/Gene Determinism
• Evolutionary/Genomic Determinism
• Systems Biology of Cancer
• Networks and Computational Biology
• Basic Molecular and Cellular Components

Required Reading

Background Book References

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![Figure 3: Computational methods in systems biology](image-url)

In this figure, we see the different methods used in systems biology. The initial data is collected through various experiments, and this data is then analyzed using computational tools. These methods are used to construct networks of molecular interactions, which can be visualized. The networks are then used to predict the behavior of the system under different conditions. This approach allows for a more comprehensive understanding of biological systems.
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)

Figure 1: Typical abstraction steps in mathematical modeling. (A) Bacteria proliferation. (B) Biological model. (C) Computational models. (D) Biological system.
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 parameter 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 (whose 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 same interval in the time interval \([t + \Delta t, t + 2\Delta t]\) for \(i = 1, 2, \ldots\).

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. \(V_{\text{max}}\) 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 \(S\).
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.

Synthetic biology and regulatory networks: where metabolic systems biology meets control engineering.
He F, Murabito E, Westerhoff HV.

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. (c) 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 in the pathway. The supply is catalysed by enzyme E1 (i.e. x1 here or enzymes stemming from an upstream operon). (d) Illustration of the steady-state properties of a supply-demand system in terms of changes in the flux, intermediate concentration and elasticity coefficients.
Figure 3.4 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 grayscale: gray means zero control, white or light gray indicates positive control, dark gray or black negative control, respectively.

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

4.1 Data for Small Metabolites 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 whether the system will reach a steady state. But numerical simulations need numerical data to assign specific values to a large number of kinetic parameters. Among these parameters are Michaelis-Menten constants, $K_m$, and maximal velocities, $V_{max}$ (for enzymes), but also biological half-lives, binding constants, metabolite 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 cases, only qualitative models can be constructed that investigate the question if a certain behavior exists at all, at least not as a unique answer. 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 predict changes in metabolite concentrations and metabolites 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 store (metabolite) data, but the process of filling these databases is currently 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 many of the kinetic data with high accuracy. Some of these techniques will be described at the end of this chapter 4.2.

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 (“bootstrap”) and the quality of model predictions can be tested by cross-validation. In Bayesian parameter estimation, parameter data is 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)
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)
Parameter Estimations

- Regression (minimum of the function)
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Methods of information theory and algorithmic complexity for network biology.
Zenil H, Kiani NA, Tegnér J.

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.

Figure 4.8. Simplifications in biochemical models. The scheme shows a branched pathway of metabolites (circles) and reactions (arrows).
(a) Omitting subunits or reactions.
(b) Replacing the values of concentrations or fluxes or relations between them.
(c) Simplifying the mathematical expressions (e.g., simplifying terms in a kinetic law, neglecting mass action parameters).
(d) Simplifying the kinetic laws, neglecting similar metabolites, protein or state of a metabolite, or metabolite concentrations in different compartments. Likewise, subsequent reactions in a pathway or elementary steps in a reaction are replaced by a single reaction of the same velocity, for parallel reactions, 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.
(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 (concentration time series, black dots) were generated by adding Gaussian noise to the 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.
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Networks

- Modules
- Nodes
- Clusters
- Interactomes
Figure 8.1: Biological networks. (a) Network of protein-protein interactions in yeast. From Tirosh et al. (b) Regulatory interactions between 41 cell genes. Genes shown as internal nodes, regulatory interactions as edges, with the biological description of the gene's main functions.

Figure 7.1: A section of the metabolic network of a "simple" bacterium. Note that each point (each chemical compound) is linked to any other point via the complexity of the network.
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.

Summary Points

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.
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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 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 $H^2$ 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: $Y_{H^2}$, the hyperbolic coordinates for the set of nodes $V$

Compute the average node degree of the network $2m$

Determine the network’s scaling exponent $\gamma$

$\beta \approx 1/(\gamma - 1)$

$R \leftarrow 2 \ln(N) - 2 \ln \left[ \frac{\exp(-e \cdot \ln(N)(1 - \beta))}{\exp(1 - \beta)} \right]$  

Compute the degree matrix $D$

$L \leftarrow D - A$

Embed $G$ to $H^2$ via $L_{X+1} \approx \lambda_{X+1} D_{X+1}$ with $k = 2$

Since the smallest eigenvalue is $0$, $Y_{emb} = [y_1 = y_2, y_2 = y_3]$

Sort nodes decreasingly by degree and label them $l = [1, 2, \ldots, N]$

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, $Y_{H^2} \leftarrow [r, \theta]$

Note that to embed a network $G$ to $H^2$, the truncated spectral decomposition of $L$ is used. This gives the closest approximation to the eigen-decomposition by a matrix $k + 1$ of rank $k + 1$, 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.

Summary Points

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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 adaption 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 size represents numbers of epistatic interactions. Aggregating and buffering interactions are shown as red and green pie slices, respectively, from Sagided [84].
Network Application Examples

(a) Gene regulatory network for Drosophila gap genes, showing relationship between input genes (Bcd, Cad, Hb, Tll) and output genes (Kni, Hb, Kr, Gl). (After figure 1 of Papatsenko and Levine (2011)). (b) Concentration of Gap genes along the anterior posterior axis of the embryo. Model was fitted to this data. Hb, hunchback; Gt, giant; Kr, Kruppel; Kni, Knirps.

The (re)volution of gene regulatory networks controlling Arabidopsis plant reproduction: a two-decade history.

A schematic of the network perturbations of one neural degenerative network over the 20 weeks of the progression of this disease in a mouse model. The red nodes indicate mRNAs that have become disease perturbed as compared with the brain transcripts of normal mice. The spreading of the disease-perturbed networks at the three different times points is striking – indicating the progressive disease perturbation of this neurodegenerative network.
Interactions between in vivo, in vitro, and computational approaches in interspecies extrapolation of toxicity perturbations. The paralogs approach, proposed by Nasev et al., 2004, and referred to by the National Research Council (National Research Council, 2006), is modified here by the incorporation of computational comparative genomics approaches. Using rat and human as examples:

1. The rat network perturbation model is developed based on in vivo data.
2. The rat and human networks are computationally compared.
3. Differences and similarities found by the interspecies network comparison are tested in human in vitro assays (e.g., primary human cell lines).
4. Quantified in vitro perturbations are mapped back to the compared network.
5. Human in vivo outcomes are informed. In addition, rat in vivo assays, driven by network-based hypotheses or otherwise (as represented by the white arrows), can inform the rat network model and the compared network model.
### “Epigenetics and Systems Biology”

#### Spring 2021 (Odd Years)

**Biol 476/576**

#### Schedule/Lecture Outline

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