The study of socioethical issues in systems biology

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ABSTRACT

Systems biology is the rapidly growing and heavily funded successor science to genomics. Its mission is to integrate extensive bodies of molecular data into a detailed mathematical understanding of all life processes, with an ultimate view to their prediction and control. Despite its high profile and widespread practice, there has so far been almost no bioethical attention paid to systems biology and its potential social consequences. We outline some of systems biology's most important socioethical issues by contrasting the concept of systems as dynamic processes against the common static interpretation of genomes. New issues arise around systems biology's capacities for *in silico* testing, changing cultural understandings of life, synthetic biology and commercialization. We advocate an interdisciplinary and interactive approach that integrates social and philosophical analysis and engages closely with the science. Overall, we argue that systems biology socioethics could stimulate new ways of thinking about socioethical studies of life sciences.

Keywords

Systems biology, socioethics, genomics, bioethics, ELSI, genetics

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Systems biology is the heir presumptive of the molecular advances made by genomics and associated high-throughput data gathering. Its mission is to integrate these extensive bodies of data into a detailed mathematical understanding of all life processes with an ultimate view to their prediction and control. Numerous governments have prioritized systems biology in their budgets for life science research and a rapidly growing body of literature identifies itself as systems biology. Despite its high profile and widespread practice, there has so far been almost no bioethical attention paid to systems biology and its potential social consequences. We will outline some of the most notable issues within a broad-ranging comparison of systems biology (including its claimed historical background and anticipated applications) with genomics and genetics and the socioethical attention they were deemed to warrant. We argue that a key characteristic of systems biology is its focus on dynamic processes. This focus should counteract a persistent tendency to interpret genomics as the science of static DNA molecules. Although we identify some novel social and ethical implications of systems biology, an even more important point of our discussion is our claim that the study of systems biology could stimulate new ways of thinking about socioethical studies of the life sciences and contribute to the development of a bioethics that does not merely follow scientific transitions but accompanies and interacts with them. We suggest that this interactive approach is more properly termed socioethics than bioethics because of its integration of social and philosophical analysis.

[See glossary for clarification of biological terms. Currently located after the conclusion.]

Systems biology

Systems biology is meant to answer the key question raised by genomics and associated data gathering: How can the field move from a list of molecular parts to a sophisticated and predictive understanding of biological processes? The realization that processes and systems do not arise in simple linear ways from genomes has forced a broadening of attention to multiple interacting levels of biological activity – none of which can be regarded as the most ‘fundamental’ (Brent and Bruck 2006). Although it uses the enormous inventories of molecules generated by genomics and other ‘omics’ (including proteomics and transcriptomics), systems biology must take such data many steps further in order to reveal the processes of life and show how systems such as cells, tissues and ultimately organisms emerge from collections of interacting molecules.[1] Most generally, systems biology aims to understand life in its most comprehensive and dynamic detail by using mathematical models to integrate high-throughput databases and experimental findings (US DOE 2005; Auffray et al. 2003). A large body of literature anticipates the ways and means by which systems biology will change biology into a more quantified and predictive activity while simultaneously overcoming the reductionism often practised in genomics (Ideker et al. 2001; Kitano 2002a). While useful at a certain phase of scientific activity, reductionist approaches are commonly argued to be insufficient to the task of fully understanding life processes (Palsson 2000; Cornish-Bowden et al. 2004).

Scientists and institutions began to gather under the banner of systems biology in the late 1990s and it is now one of the biological funding priorities in Europe, the US and Japan (US Department of Energy 2005; WTEC Panel 2005; Reiss 2005). Two foci of systems biology are human health and environmental remediation by

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[1] In an earlier discussion of the philosophical issues in systems biology, we described two overlapping strands of scientific activity: the majority pragmatic approach, which connects molecules into systems from the bottom up, and the minority systems-theoretic approach, which works from top-down system principles to understand molecular interactions (O’Malley and Dupré 2005).

microbes (bioremediation). Biomedical researchers anticipate the development of computer models that will integrate biological data from multiple levels for predictive diagnosis, treatment and prevention of disease (Hood et al. 2004). These models will encompass detailed understandings of molecular mechanisms, the effects of perturbing particular processes, and the correlation of biomarker patterns with disease states (Ideker et al. 2006; Mustacchi et al. 2006; Kitano 2004a; Waters and Fostel 2004). It is anticipated that models of human systems designed for drug discovery and development will dramatically improve the disappointingly low rate of successful verification of the medical effectiveness and safety of chemical compounds aimed at drug targets identified from genome sequences. The failures in this area have been attributed to the lack of biological insight accompanying sequence discoveries (Butcher 2005; Hood and Perlmutter 2004; Noble et al. 1999). Bioremediation research informed by systems biology expects to integrate multiple levels of molecular and microorganismal interactions and design microbial systems able to remedy pollution in areas important to humans (Pazos et al. 2003; Lovley 2003). While microbial effects on environments have long been known (as have numerous drug targets in humans), advocates of systems biology argue that the precise interactions they enable and their side-effects cannot be properly understood without systems analysis.

For some commentators, systems biology is just old wine in new bottles. They see it as either a revitalized form of physiology (e.g.: Bothwell 2006; Strange 2005) or the youthful descendant of an aspiring enterprise that emerged in various forms over the last four decades under the aegis of cybernetics, systems engineering or self-organization theory (Westerhoff and Palsson 2004; Huang 2004). ‘Predecessors’ such as von Bertalanffy’s general systems theory or Robert Rosen’s mathematicization of system organization and maintenance are often invoked and very occasionally applied (e.g.: Cornish-Bowden and Cárdenas 2005; Wolkenhauer 2001). While it remains to be seen how distinctively different current systems biology is from earlier approaches and how successful it will be in its own right, there is no doubt that the quantity of data it is already integrating, and its emphasis on mathematical modelling of interacting molecules and their emergent properties, constitute a shift from earlier genomics and genetics approaches, as well as from earlier higher-level functional approaches such as physiology (Ideker et al. 2006). And, even if it is important to bear in mind the historical context of systems biology, earlier forms of systems-theoretic biology were neither very practical nor biologically informed (Kitano 2002b). Contemporary systems biology appears already to be both of these.[2] At the very least, the sheer volume of molecular data available to contemporary systems biologists may suffice to transform a difference of degree to a difference of kind.

Social commentators may be disturbed by what they perceive as the exaggerated claims of systems biology and what it can and will deliver, especially in respect to human health. A similar rhetoric accompanied the development of genomics and many of those promises have still to be realized (McGee 2003). That disappointment, however, lies with genomics practised primarily as a sequencing endeavour. Systems biology will arguably realize genomics as a fully fledged science, in which true biological insight is gained by using a variety of tools to integrate DNA data with many further levels of biological information. Nobody is promising immediate biological enlightenment and instant cures with systems biology. Many advocates temper their convictions that systems biology is already making contributions to biological knowledge and therapeutic interventions with explicit acknowledgements of how far the field has to go before it achieves a genuine capacity for prediction and control (e.g.: Cassman et al. 2005; Butcher et al. 2004; Mustacchi et al. 2006; Cornish-Bowden 2005).

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[2] We base our simple assessment of practicability on the proliferation of literature about the importance of systems biology's findings (Bork 2005) and the amount of funding and science policy recognition the field has achieved internationally (WTEC 2005). More subtle assessments of what constitutes success in respect to contemporary systems biology will have to wait for a longer-term analysis of the achievements of newly created institutions of systems biology, the published findings they produce and their impact on associated subfields of biology.

For many scientists, it is systems biology's inextricable commitment to multidisciplinary investigation that provides the greatest challenge to its future success (e.g.: Hood and Perlmutter 2004; Liu 2005; Kling 2006). A truly integrated combination of insights and tools from a number of biological, mathematical and computational disciplines is central to every anticipated achievement of systems biology. Although interdisciplinarity is frequently raised as an issue of social organization, almost none of the broader discussions of systems biology yet addresses the socioethical issues that may arise with the development of the field, despite the fact that such issues were key concerns of the human genome sequencing projects.

From the ELSI of genomics to the socioethics of systems biology

The Human Genome Project (HGP) had an embedded programme for ethical, legal and social implications (ELSI) that allowed the exploration of a plethora of bioethical questions ranging from privacy concerns to the commercialization of life (Patrinos and Drell 1997; see also Table 1, Column 1). Although social scientists and philosophers often criticized HGP ELSI for its lack of autonomy from the science (Clayton 2001) and scientists attacked some of its projects for their triviality and irrelevance (Marshall 1996), the ELSI investigation of genomics nevertheless flourished and expanded within the sphere of human genomics. There was very little ELSI attention to spare for the genomics of other organisms (we will attempt to show below the benefits of expanding this focus in systems-based socioethics), and the issues raised were not, overall, conceived to be that different from the social and ethical issues raised by genetics (e.g.: Robertson 2003). Just as genomes were supposedly straightforward amplifications of genes, so the ELSI study of genomics was mostly considered an amplification of the study of ethical, legal and social studies of genetics.

Genome sequencing, however, is only the barest beginning of research that might eventually realize socioethical concerns, whereas systems biology is currently considered to be the most promising scientific vehicle for bringing such implications into being. Why, then, is systems biology so far exempt from social and ethical considerations? We believe the main reason that there are at best minimal gestures towards socioethical programmes in systems biology manifestoes (e.g.: US DOE 2005: 79, 196) is because the scientific object in question is a far more elusive set of processes than the object initially sought in genomics. Although ELSI discussions of genomics were often critical of metaphors equating genes or genomes with blueprints or programmes for life (Nelkin 2001), many of these analyses nevertheless addressed genomes as if they were static definable entities that ultimately determined the properties of organisms and human nature (Ashcroft 2003; Lewens 2002; Richards 2001). Although some scientists contributed to this view (see Suter 2001), the science itself was rapidly unable to sustain such genomic determinism. Sequences were obviously not *the* answer to questions about life but merely contributors to the parts list that could be used within a more integrative process-focused approach (Bains 2001; Brent 2004).

Systems biology's core concept of a system is far fuzzier than that of a genome sequence (O'Malley and Dupré 2005; Fox Keller 2005).[3] Systems are generally conceived of as dynamic processes but currently anything from a few interacting molecules to entire ecosystems may be covered by the label (Hood and Perlmutter 2004). While systems can be mapped on to a hierarchy of biological objects, such as cells or organisms, the concept is not so restricted as to exclude a range of subcellular 'systems' (e.g.: biochemical pathways, genomes) or metaorganismal 'systems' (e.g.: cooperative bacterial communities). The range

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[3] There has been little ontological discussion about genomes amongst scientists or bioethicists. Scientists have tended to restrict their abstract discussions of genomes to the metaphors used to describe them (e.g.: Avise 2001), whereas philosophers of biology have reserved their fascination for gene concepts (e.g.: Stotz et al. 2004 – although see Dupré 2004 for some speculations about ontological problems concerning the genome).

of properties that systems must have (e.g.: robustness) and how these will be detected is a growing sub-theme of systems biology (e.g.: Alon 2003; Csete and Doyle 2002; Kitano 2004b). Through an understanding of these properties, some systems biologists believe they will come to know their objects (systems) more fully than can be achieved by narrow focus on the components of the systems.

The complex nature of systems complicates attempts to envision the ethical, legal and social issues that will be raised by systems biology, and may lead to the view that the investigation of any such issues can be deferred. Although it is unlikely that anyone will argue that systems biology is free of social implications, we believe it is also unlikely that issues raised with respect to the HGP and associated genomic projects could be carried over to systems biology without significant rethinking. If we take systems to be entities that encompass sets of dynamic interactions and then compare this notion to the static qualities often attributed to genes and genomes, we can gain an initial sense of the ways in which novel or reconceived socioethical issues might arise in relation to systems biology.

TABLE 1: Static versus dynamic socioethical approaches

Socioethical issue	**Static genocentric interpretation**	**Dynamic systems reinterpretation**	**Consequences of reinterpretation**
Identification, privacy and discrimination E.g.: Insurance or employment discrimination because of genetic test results; civil liberty infringements (Greely 1998; Anderlik and Rothstein 2001)	DNA dictates health status and because it is biologically 'exceptional' its investigation must be covered by special regulation (Suter 2001)	Health and illness are both dynamic states which result from complex interactions of multiple genes, other molecules and environmental factors	Genetic tests say very little about biological mechanisms and processes, and in the context of multilevel biological insight, genetic 'exceptionalism' is a fallacy
Identity and ancestry E.g.: Conflation of social and biological classification (Brodwin 2002; Foster and Sharp 2002) Genomes as souls (Mauron 2001)	DNA is a fixed marker of ancestry and identity and the most fundamental repository of humanness	DNA is one of the many constituents of our biological make-up, and multilevel interactions and emergent properties are much more likely to give us insights about human characteristics	Relying on DNA to reveal identity, ancestry and human nature will lead to an impoverished understanding of ourselves and others
Genome modification and the integrity of life E.g.: Environmental contamination; violation of nature (Nuffield Council on Bioethics 1999; Reiss and Straughan 1996)	Because genomes are the fundamental basis of life, changing any part of the genome will change the organism in a fundamentally 'unnatural' and negative way	The organism is a product of many interactions, including natural genetic engineering	Genetic engineering is a complex process that must be understood in a broader biological context
Ownership and commercialization of genes, genomes and genetic information E.g.: Who owns individual genetic information? Is life ownable? Does DNA patenting block further research? (Robertson 2003; Rifkin 1998; Heller and Eisenberg 1998)	A gene is a discrete and ownable stretch of DNA with clear causal properties	A gene's effect is contingent on genomic, cellular and other environmental contexts. If DNA as information is patentable, then a hierarchy of biological information has also to be considered patentable	The current gene patenting paradigm cannot deal adequately with systems understandings of DNA and other biological material

New socioethical themes in systems biology

Although Table One gives a general sense of how *not* to think socioethically in relation to systems biology, a more constructive discussion is also needed about new socioethical issues that arise in and around the field. Very little work has been done on any of these, but there is a small body of literature (or extrapolations that can be made from it) that allows us roughly to parallel the ‘old’ genomics categories in the table with ‘new’ systems biology ones. Each category, however, takes on different dimensions in relation to systems approaches and some of the following discussion – because of the immaturity of systems biology – is necessarily anticipatory and prospective. Nevertheless, if the bioethics community shifts its attention away from genomics and genetics to systems biology, it will have to address at least the issues we raise below.

In silico **testing**

The ethics of testing in the form of privacy and discrimination concerns were a major bioethical theme in genetics and genomics,[4] but it is very probable that systems biology will give rise to some rather different questions about testing. One of the most attractive aspects of systems-biologic approaches for industry is the science’s much touted capacity to move experimentation on living organisms or *in vitro* biological material to computer simulations of biological systems (Mack 2004; Mucke 2005). It is anticipated that *in silico* drug testing – not the province solely of systems biology, but an important component of it – will allow extensive understanding of side-effects and benefits of chemical interventions before standard clinical trials. It could thus achieve a huge reduction in the current costs of drug development, even as markets fragment towards pharmaceutical products for sub-populations and possibly individuals (PricewaterhouseCoopers 1999; Musante et al. 2002; Butcher et al. 2004). Many of the companies that

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[4] McGuire and Gibbs (2006) discuss how systems biology may straightforwardly increase privacy risks.

presently advertise systems-biological approaches are exploiting a range of *in silico* capacities to simulate disease courses and therapeutic responses to simulated interventions at discovery, pre-clinical and clinical stages (e.g.: Stokes and Arkin 2005; Mack 2004; Uehling 2003).

A key socioethical issue that needs to be considered in relation to this aspect of systems biology is whether *in silico* testing will ever have the same legal status as *in vitro* or *in vivo* tests, or whether *in silico* results will always require non-simulated experimental confirmation. The political and economic advantages of side-stepping animal testing have often been seen as one of the significant social advantages offered by systems biology (e.g.: UK Engineering and Physical Sciences Research Council 2004; Noble et al. 1999). This commonly perceived benefit may, however, become complicated by doubts about the trustworthiness of transferring *in silico* results to *in vivo* treatment. We anticipate, however, that the possibility of minimizing clinical trials based on animals will be one of the most warmly welcomed social benefits of systems biology.

Cultural understandings of life

A broad area of enormous interest for future socioethical commentary will be the translation of systems biology into what we call cultural understandings of life. This category encompasses and possibly transforms the identity and ancestry themes that arose in earlier genomics. The shift from perceiving the essence of life to be encapsulated by a static material thing to seeing life as a fluid and complex process in dynamic environments is a major one. Although this change is a premise of systems biology rather than its outcome, the increasing visibility of systems biology could have a major role in increasing public understanding of this insight. Of course, given the continuing vagueness of the concept of a system, it may be argued that systems biology is unlikely to capture the public imagination at all (e.g.: Wynne 2005). Instead, its subtle claims of complexity and emergence may be overwhelmed by traditional assumptions of reductionism and determinism because of systems biologists' insistence on the prospects for greater prediction and control. Misleading but powerful simplifications of the nature and function of DNA have persisted throughout the genomics era (Ashcroft 2003) and cultural translations of systems could also attribute supreme determinative status to DNA or other molecules.[5] The sophistication of systems biology's shift away from the focus on DNA sequence to more complex biological processes may not be exactly reproduced in public discourse but it need not take the 'simplistic determinism' avenue of interpretation. The notions of 'whole' and 'complete' that accompany scientific talk about systems (e.g.: Selinger et al. 2003) could easily prove at least as culturally attractive as genetic reductionism, and even a loose consideration of systems could change some linear and unicausal ways of thinking about the natural world.[6]

One example of the antidote offered by this extended view can be found in metagenomics, which is the study of the DNA of entire microbial communities in natural environments (Handelsman 2004). Although currently mostly about sequencing and gene discovery, the ultimate aim of metagenomics is to study the DNA of communities of organisms (rather than individual genomes) and community interactions from an integrated systems perspective (Rodríguez-Valera 2004; DeLong 2002). These system-based understandings will further illuminate the extensive commensalisms between, for example, humans and microbial communities (Nicholson et al. 2004; Bäckhed et al. 2005; Relman and Falkow 2001), and demand an appreciation of the deep interdependences within

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[5] One epistemological point we would emphasize here is that although systems biology does aspire to prediction and control, its predictiveness is not simplistically deterministic. Systems biologists do want to understand causal relationships but these are repeatedly acknowledged (through the bitter experience of research failure rather than philosophical conviction) to be about complex loops of interaction that resist linear causal modelling. Systems biology models will be able to specify the 'possibility space' for system behaviour rather than make exact predictions of a single behaviour (see Palsson 2000 for a good discussion). There are, of course, different strands of systems biology and some are narrower than others, but we doubt any future historical overview of systems biology will find that its practitioners adhered to simplistic reductionist and determinist analysis.

[6] While popular forms of holist thinking do exist (Lovelock's Gaia hypothesis amongst them), systems biology in scientific discourse restricts itself to definable systems which are tractable to modelling and simulation. Overall, these systems are rather resistant to the language of goals and intention that usually accompanies the more mystic views of large systems (Volk 2006).

the biodiversity that constitutes the human body.[7] Although microorganisms have not commonly fallen into the category of life-worth-caring-about for many members of the public and even non-microbiological scientists (Nee 2004), the widely publicized achievements of early metagenomics (e.g.: Venter et al. 2005; Tyson et al. 2005[8]) and their potential to reconfigure ideas about how life is organized may change public indifference. Broader discussion of microbial systems might also lead to a different conservation ethic, in which interacting components and levels are more carefully appreciated than is captured in conventional talk of 'the environment'. More generally, we believe that a systems biology socioethics will find it hard to justify a purely human focus, even if human health research retains its paramount focus for bioethicists.

Biological modification

Cultural understandings of life lead directly into the next issue, which shifts the concern from what life is to what can be done with it. The consequences of biological modification was an ELSI topic of enormous importance for the reception of genomic technologies and products, most damagingly exemplified in the GM controversy, which – in Europe at least – led to the failure of several lines of crop research and commercial products (Rifkin 1998; Frewer et al. 2004). One possible achievement of systems biology will be to give scientists the capacity to synthesize and intervene in life processes in radically new ways in the forms of synthetic biology (Church 2005; Benner and Sismour 2005) and nanosystems biology (Heath et al. 2003; Zandonella 2003). Although systems biology is not identical to or necessarily inclusive of synthetic biology, the two connect in their conceptualization of systems as 'designed'[9] and engineerable (Brent 2004). Synthetic systems research may eventually combine with the development of

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[7] For further discussion see O'Malley and Dupré (in press).

[8] Popularly cited examples of metagenomics include Venter et al's vast inventory of genes in the Sargasso Sea and Tyson and colleagues' analysis of the metagenome of the microbial community living in highly acidic mining sites.

[9] This attribution of design is not a metaphysical one (as intelligent design 'theory' is) but an epistemological approach to system understanding that attracts a different range of criticisms (see O'Malley and Dupré 2005).

artificial molecular machines that mimic all aspects of life processes (Drexler 2005) and thereby raise profound questions about the creation of artificial life.

While the interface between synthetic biology and systems biology is frequently talked about in regard to human health (e.g.: Kitano 2002a), it has also excited a great deal of environmental and microbiological attention. Eco-engineering, or bioremediation achieved by stimulating indigenous microbes (rather than modified lab cultures) to degrade pollutants, is anticipated as a solution to the older and frequently unsuccessful approach of genetically engineering microbes. The latter involved 'DNA cut and paste exercises' couched within greatly simplified understandings of biological processes (Cases and de Lorenzo 2005; Sayler and Ripp 2000). Eco-engineering depends on better knowledge of system processes and how the activities of natural communities of interacting organisms can be enhanced to decontaminate a wide variety of ecosystems (Pazos et al. 2003; Newman and Banfield 2002). The scientific shift from genetic engineering to eco-engineering (or systems engineering) is an important one, and it may enable a different discourse about the social consequences and concerns of such interventions. A broader view of genetic engineering – a view that would include the extensive horizontal gene exchange that occurs naturally in microbial communities – is a potential social side-effect of a more public discussion of eco-engineering research. Molecular insights into ecosystem interactions would not necessarily change ideas about the acceptability of genetic modification but they may change some of the ways those arguments are attacked and defended.

Current discussions amongst scientists about social and ethical issues in synthetic biology take a traditional focus on developing safeguards to prevent the loss of control of engineered cells and organisms (Pennisi 2005; Check 2005; Ferber 2004). The potential social concerns go much deeper and wider than risk analysis, however, and are connected to the implications we noted above for a general cultural understanding of life based on systems. These understandings are likely to resonate with a range of ideas about modification and its acceptability. Although much of the engineering and synthesizing of cells, organisms and environments will happen at the microbial level (US DOE 2005) – and microbes, as we have noted, often evoke little interest beyond concerns about possible pathogenicity – public sensitivity to human, other animal and plant applications is likely to be high. There is a widespread Western cultural distaste for engineering metaphors when applied to living entities and life processes (Fujimura 2005), and systems biology often insists upon and indeed celebrates an engineering perspective (e.g.: Ideker et al. 2006; Brent 2004; Csete and Doyle 2002). The whole notion of synthetic biology brings up deep metaphysical questions about life and what is entailed by the artificial creation of living entities from ‘non-natural’ constituents or the introduction of unnatural activities in naturally existing organisms or communities. While these are challenging issues for which we have no ready answers, we believe that a discussion informed by systems understandings is likely to be more realistic than one premised on a static notion of a genome. However the debates over synthesized microbial cells are managed, they will have immensely important consequences for the distant future when synthesized human cells are created.

Commercialization

Commercialization, the last of the socioethical themes in genomics distinguished above, provides a good illustration of the complexities a systems-biologic perspective introduces to social and ethical discussions of science. When DNA sequences were first patented they were treated just like any other chemical compound, as ‘compositions of matter’ with obvious causal properties. We have seen a movement away from this chemical analogy in a few patent applications which have attempted to claim genomic sequence in computer-embodied or ‘informational’ form (O’Malley et al. 2005; Maschio and Kowalski 2001). Systems biology is perceived by a number of scientists and commentators to be primarily an informational science (e.g.: Hood and Galas 2003; Allarakhia and Wensley 2005), in that it is built on knowledge of multiple biological levels and its discoveries and applications are going to be achieved computationally. These commentators argue that systems biology will radically push the patenting and commercialization process further away from biological material and towards information (Allarakhia and Wensley 2005; Hood, in Compton 2001).

There have already been a few successful patent applications in systems biology and a great many more are pending (Russell 2006a; Nature Biotechnology 2005). However, it is not clear that these patents and patent applications are attempts to gain ownership of biological information in the same way that patents of DNA sequences are. Most existing systems biology patents and applications are for computer tools that use biological information in order to make predictions and effective interventions.[10] The patents are therefore mathematical representations of biological processes (conceived of as systems). They manipulate information and make it clinically or scientifically meaningful (Russell 2006a; Goldman 2002). Some of these biosimulation tools carry names such as ‘Virtual Patient’, ‘Virtual Human’ or ‘Visual Cell’ (Uehling 2003). They are not yet very sophisticated but are already achieving useful results, showing, for example, the likelihood of adverse side-effects before expensive drug development is initiated.

If we think about systems biology patents in the context of public concern about DNA and other biotechnology patents, there are several potential broader social responses, both negative and positive. On the negative side, because models in systems biology may be perceived as approximations of ‘life itself’, their commercialization could be interpreted as a greater threat to conceptions of the integrity or sanctity of life than was the patenting of DNA sequence. Also on the negative side, computer-generated models have many similarities with computer software, the patenting of which is highly contentious because of fears of monopolization by large corporations (Perchaud 2003).

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[10] Other ‘systems’ patent applications, however, appear to revert to traditional composition of matter patents and claim interacting molecules rather than anything obviously informational (see Allarakhia and Wensley 2005, Table 2).

There are more positive possible social responses to the commercialization of systems biology, however. Since systems biology will involve the patenting of representations of biological entities rather than the entities themselves, systems-biologic patents may allay the concerns raised above about the private ownership of life. Systems biology could thus transform biological patenting into a less contentious activity – at least until the advent of the next wave of systems biology patents and commercial products, which will possibly be based on synthesized life processes. With the rise of synthetic biology alongside systems biology, patenting may bifurcate into the computer-based tools produced by systems biology and the material objects produced by synthetic biology. The commercialization of the latter will sharpen general public discussion about synthetic life and its relationship to natural living systems.

A further issue that bears on the social concerns about what is and should be ownable is the anticipation that systems biology patents may severely constrain the data-sharing that is necessary for the science to develop. When interconnected levels of system models are covered by different patents, the result may be ‘patent thickets’ that inhibit research and deter innovation. The situation Heller and Eisenberg (1998) famously called the ‘tragedy of the anti-commons’ in relation to genomic research could thus be greatly exacerbated in systems-biologic research because the study of biological systems requires even greater cooperation and collaboration of many different specialist groups than did genomics (Rai 2005).

For these reasons, the ownership and commercialization issues raised by systems biology could be interpreted to demonstrate that an overhaul of the intellectual property regime in relation to biological inventions is long overdue (Hood in Compton 2001). Collaborative ownership regimes[11] may be a more

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[11] Open source is one such collaborative ownership regime that could be considered. In bioinformatics, much existing software is open source and this is also the case for emerging systems biology software (such as Systems Biology Mark-up Language). Research findings made at the lab bench may be more difficult to fit into this mould, however (see Rai 2005).

practical alternative in the age of large, highly collaborative biological research programmes. For example, some systems biologists and commercial developers are talking of setting up an international database for computational models in which models would have to be made freely accessible or scientific papers based on them would not be accepted for publication (Russell 2005; Stokes and Arkin 2005).

An opposing view, however, is that radical changes to the existing intellectual property regime are not necessary, and that modifications of the current system would be sufficient to ensure that patents in systems biology avoid some of the problems created by genomic patenting. For example, some companies have been granting non-exclusive licenses for their biosimulation tools (e.g.: Gene Network Science's 'VisualCell'). If broad licensing becomes general practice in the commercialization of systems biology, research obstruction may not occur. Another suggestion is that the best way to deal with developments in systems biology is to make sure that inventors do not take out overly encompassing patents, which – if granted – could be extended in the future to cover presently unknown functions of the invention (Allarakhia and Wensley 2005). Overall, however, the novelty of systems biology means that few of the commercialization issues are yet obvious and straightforward. At this early stage, the main point we would make is that socioethical engagement with systems biology's commercial potential could influence its development, and thereby achieve more than would post-hoc descriptive work.

Concluding reflections on the socioethical study of systems biology

All these developing issues, while foreshadowed by earlier ELSI and bioethical treatments of genomics, take the discussion into new realms that are potentially topics of great mutual interest for scientists, the general public and social commentators. The socioethics of systems biology may, however, require even more than an agenda expansion and reorientation of ideas. We believe systems biology challenges some assumptions about how the implications of scientific developments should be studied. We argued earlier that the dynamic nature of systems meant that approaches concerned with static genes and genomes would not be adequate, but here our argument for a different approach focuses on the organization of the science – most specifically in regard to the interdisciplinary and interactive nature of the inquiry appropriate to systems biology.

Systems biology is interdisciplinary not for its own sake but in response to perceived scientific imperatives; similarly, systems biology bioethics may have to make genuine and transformative interdisciplinary analyses in order to understand its complexly interacting objects. Interdisciplinarity does not mean that all disciplines contribute equally or indistinguishably to the inquiry, but that different lines of investigation provide enhanced understandings of the complex phenomena with which the field is concerned. Jason Robert (2005) thoughtfully anticipates this necessity in what he calls 'systems bioethics', which – although generally about a systems approach to the bioethical study of any life science – embraces a wide-ranging socially contextualized study of bioethical issues that is highly appropriate for systems biology itself.

Although there has been considerable discussion about the integration of social scientific inquiry and bioethical reflection (e.g.: Light and McGee 1998; Zussman 2000; Hedgecoe 2004; Borry et al. 2005), a considerable distance has been maintained between the two in spite of and perhaps even because of that debate. In our view, this separation is not a sustainable one and that is why we use 'socioethics', rather than bioethics, to describe the potential study of systems biology. All of the issues we raise above show how ethical analysis cannot be conducted in isolation from sociocultural context. In other words, ethical analysis is always localized, with its very questions the product of specific social and cultural circumstances. Each issue has important social dimensions, both in the ways it is constructed and the ways it may be addressed. This is obvious even in this highly prospective analysis of systems biology issues, and we do not expect them to become simpler as the capacity of the science increases and public attention to it grows.

Not only do we advocate much closer interdisciplinarity, but also a process of inquiry that is more interactive – not just between social scientists and bioethicists but between socioethicists and scientists.[12] In the old bioethics or ELSI paradigm, the role of social scientists and ethicists was to ask, 'Here is the science: what are its implications?' We acknowledge that some contributors resisted notions of a clear line of demarcation between natural and social worlds and a linear flow from one domain to the other (Brown et al. 2000), but that was not the standard approach to inquiry. We believe a more valuable socioethical approach to systems biology would study systems biology as it develops, rather than waiting until the science has already set its course. Because systems biology socioethicists would have to study ongoing and emerging research, they would need to have close connections with the scientists themselves – something we have found systems biologists are open to because of their genuine sensitivity to many of the issues we have described.[13] The tightrope of being either too close to or too far from the science (Nature Editors 2006; Pilcher 2006) is one that we believe can be navigated, but it requires a new way of thinking about the involvement of bioethicists – one that goes beyond the 'ethical advice' model. As well as providing better engagement with the research itself, an interactionist approach also helps anticipate (and to some extent shape) the emerging social issues. This engagement also has the potential for the mutual transformation of the ideas of both the scientists and those who study them.

Take, for example, the issue we highlighted above of creating life. We noted that at present, scientists are grappling with 'social' issues of synthetic biology, and

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[12] Even very sophisticated socially contextualized arguments often slip into a simple biology-versus-society (or culture) framework (e.g.: Levy and Lotz 2005).

[13] We are currently engaged in a sociological study of the institutionalization of systems biology in the UK, US and Japan.

that these are largely perceived as those of anticipating and preventing the potential harms of creating novel life forms. One obvious problem is to decide what constitutes such a creation as a living entity. It is not enough for scientists to come up with a technical definition of life that fits their scientific context. They also have to take into account the deep public unease – in most cultures, however differently grounded – with the very idea of creating life. Risk analysis and control are secondary to and probably dependent on finding and working effectively with a concept of life that meets the expectations of different social groups, although such concepts cannot be imposed by any one of these groups. And, as much as careful socioethical analyses of 'life' may shape scientific agendas, so scientific work may change broader cultural expectations of how to understand life and interventions in it. Conceptual negotiation will be the only way in which the profound and contentious issues of synthetic systems will be productively discussed. We anticipate, therefore, that such interactions will have to be iterative, with the provision of appropriate forums for negotiation between scientists, socioethicists and other social groups.

In this context of understanding interaction, it is important for the bioethics community to consider the broader cultural impact of its representations of the science. It is worth reflecting how ethics-based critiques of DNA research appear to have reinforced genocentric thinking and squeezed socioethical discussion into a very narrow framework. In addition, the bioethical and social scientific focus on human genomics may have taken public attention away from numerous other aspects of genomics, such as comparative and microbial genomics. A better grasp of systems biology – at all levels of biological organization – could prove an antidote to this tendency and the arbitrary limits it imposes on an engagement with the science.

Overall, we believe that socioethical engagement with systems biology offers an opportunity for a new approach to asking and answering social questions in science, in which much closer collaboration between those concerned with the life sciences could underpin scientific, social, legal, ethical, political, cultural and economic discussion. Interdisciplinary interactive collaboration could fundamentally change the relationships between life scientists and those who study them, as well as the way we think about bioethics.

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GLOSSARY	
Biomarker	A biological characteristic (often molecular) used as an indicator of a larger biological process (normal, disease related, or a response to therapy)
Bioremediation	The use of microorganisms to remove contaminants from environments through the chemical reactions involved in microorganismal metabolism
Biosimulation	The use of computer models to conduct virtual tests of hypotheses on simulated biological entities and processes
Drug target	Molecules (mostly proteins) that are identified as disease relevant and made the therapeutic target of introduced chemical compounds (drugs) in order to change the disease process
Genocentric	A perspective that places DNA (genes or genomes) at the centre of attention, and as causally primary in biological systems. Usually used pejoratively
Genome	All the genetic material of an organism
High-throughput	The use of automated equipment and software to describe rapidly and comprehensively all the elements of a biological entity (such as genomes) or to conduct large-scale experiments (e.g.: screening hundreds of drug compounds against drug targets)
In silico	Created or modelled on a computer system
In vitro	The study of biological material in a test tube or other experimental setting rather than in an organism (*in vivo*)
Metagenomics	The study of the DNA of microbial communities in their natural environments (*in situ*)
‘Omics	A suffix or stand-alone word that indicates a study of the complete set of components involved in different levels of cellular and organismal activities
Proteomics	The study of all the protein products of a genome in an organism (or cell) in a particular set of conditions
System	A higher level entity that emerges from the interactions of components of a biological entity.
Transcriptomics	The description and analysis of all the expressed (or ‘transcribed’) elements of a genome in specific conditions

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