Systems-Science and Biology
Exploiting Creative Tensions

TCC Workshop

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Preamble

“Making sense” of biological organization

- Want “high level” perspectives that can integrate and do justice to biological “detail”.

- Widely-held view: Current conceptual frameworks of systems-science and biology are “in principle” adequate. Obstacles are largely technical and computational.

- Significant successes, both in “reverse engineering” and in introduction and investigation of high level concepts (e.g., robustness, evolvability).

- But will such approaches suffice ?

A not so recent line of inquiry !

...We are faced with a great series of wonderful systems, differing slightly from each other and maintaining themselves in slightly different surroundings. But we have no proper scientific words with which to talk about them. For example, it is absurd that this book contains so little reference to genetics, biochemistry, or control theory. No doubt this is partly my fault, but the fact is that these more exact sciences have yet to show us how to treat the organization of a whole creature.

from J.Z. Young
preface to the second edition of
The Life of Vertebrates
Oxford University Press, 1962
New York & Oxford

Claims

- Current metaphors of systems-science -- control, communication, computation -- don't suffice. Need to incorporate additional metaphor: coherence. (Also coherence-maintenance / coherence-imposition).
- Problems of "coherence" and "coherence maintenance" are ubiquitous for biological systems, and are central to making sense of biological organization.
  - Need theory/praxis that emphasizes and thematizes these problems.
  - Will require its own conceptual and technical tools. Can't simply piggy-back off existing approaches. Can't express within existing technical vocabularies of the various "more exact sciences".
  - Analogy: Concurrency
    - "You need new language to express concurrent activity, and new theory for it. You cannot decently express it as a metaphor in a sequential language." -- Robin Milner, 1997 Turing anniversary lecture.

Claims (cont'd)

- Biological "modes of coherence" are different from those of designed systems ("standard modes of coherence").
  - Intriguing intermediates: quasi-evolved systems such as Internet
- The "more exact sciences" -- insofar as they address coherence issues -- are biased towards standard modes of coherence.
  - Inherent tensions / mismatches between "more exact sciences" and biological modes of coherence.
  - My belief: Radical reorientation -- conceptual and technical -- will be needed to accommodate biological modes of coherence.
- Strategy: Exploit these tensions.
  - Elucidate distinctive character of biological organization.
  - Derive pointers to necessary reorientation.

Aims of presentation

- Clarify what I mean by “coherence”.
- Elaborate on, and offer evidence for, the preceding claims.
- In particular, suggest ways to exploit the aforementioned “tensions”.
- Solicit feedback.

Caveats

- Genuinely “technical” treatment of coherence still largely out of reach.
- No theorems, or even precise definitions.
- Arguments and evidence via examples and hand-waving.

Coherence

“Definition” and generalities

Coherence

- A portmanteau term intended to call attention to -- and to express -- how the system's organization "makes sense" / imposes sense.

- Deliberately ambiguous and elastic, so as to accommodate a necessarily open-ended multiplicity of related senses.
  - Examples: wholeness, rationale, non-arbitrariness, consistency, homeostasis,…

- One very large class of coherence maintenance problems: Problems of coordination / matching under conditions of decentralized control.
  - In particular, in contexts with multiple, only partially compatible control objectives.
  - Most interesting contexts: where very notions of "control", "control objectives" are problematic.

Coherence (cont'd)

- Allows formulation of new types of "why" questions.
  - "Why is aspect X of system organization the way it is ?" is reframed as "How does aspect X impact on the coherence of the system ?".

- Different from "What does aspect X optimize ?".
  - In particular, coherence criteria needn't be quantifiable, let alone scalar.

- Different from "What is the function of aspect X ?"
  - Don't presuppose linear cause-effect framework of explanation.
  - Instead, webs of heterogeneous influences, not necessarily reducible to a common currency.
  - Multi-factorial, multi-perspectival.
  - Non-modularity, multi-modularity.
  - "Function" is only part of the story.

Coherence (cont'd)

Caution:

- No reason to expect universal lexicon able to express all relevant criteria of coherence for all possible systems of interest.

- In any particular context of interest, cannot presume relevant coherence criteria to be known in advance. Part of the enterprise is to discover what they are.

- Only certain coherence criteria can be expected to be quantitative.

- Most importantly, there may be limitations of principle as to degree of sharpness with which various relevant coherence criteria can be expressed.

  - Not a matter of "imprecision", but of contrast between type of precision achievable via natural languages vs. formal languages.

  - Not a shortcoming. May reflect necessity to "leave room" for the unanticipated and unanticipatable.

Example: the Internet

“ [The designers of the Internet architecture] experienced great difficulty in formalizing any any aspect of performance constraint within the architecture. These difficulties arose both because the goal of the architecture was not to constrain performance, but to permit variability, and secondly (and perhaps more fundamentally), because [although there were formal tools available for verifying logical correctness of the protocol with respect to specification] there seemed to be no useful formal tools available for describing performance.”

David D. Clark,
writing to explain “why the [TCP/IP] protocol is as it is”.
(The design philosophy of the DARPA Internet protocols, SIGCOMM 1988).

Basic questions

- What are the “modes” of coherence of the system ?
- How does the system impose and maintain coherence ?
- In what ways can coherence breakdown ?

Meta-questions

- In what terms can we describe / characterize the system’s coherence ?
- What can qualify as an answer to the basic questions ?
- What kind of theory is possible ?

Basic questions (cont'd)

- These questions are interrelated.

- Example: Our view of what cognition "is", or "how it works" is closely tied to what we regard as its potential disorders.
  - Far from theory-neutral.
  - In this context, disorder may result not in absolute breakdown, but in transition to alternate modes of coherence. Shift of cognitive style.

- Example: The notion of "programming model", as defined in NRC 2005 report: The future of supercomputing.
  - "A programming model is an abstract conceptual view of the structure and operation of a computing system. For example, a uniform shared memory (or global addressing) model supports the abstraction that there is one uniformly addressable storage (even though there may be multiple physical memories being used). The use of a given programming model requires that the operating system, the programming languages, and the software tools provide the services that support that abstraction."
  - Thus, our view of the programming model impacts on what we regard as a potential breakdown in service.

Coherence

Examples

Example: organism as network of heterogeneous constraints

- Constraint-network picture objectifies organism as “global” entity.
  - Constraints are couplings and relations among components, subsystems, organizational levels. Express how “global” entity is “glued together” out of “local” parts.
  - Heterogeneity of constraint-network reflects cellular / molecular diversity of organism. Also, multiplicity of signaling systems, control motifs, organizational levels.
  - Emphasis on inherent overlap, entanglement, and cross-cutting vs. clean hierarchical or layered architecture.
- Integrative character / coherence of network gets reflected in non-arbitrariness of the “gluing”, i.e., in limitations of principle on how system can be “put together”.
  - Look for compatibility relations among the constraints; alternately phrased, for “higher order” constraints that must be satisfied for “self-consistency”.
  - Probe “rationale” of system by viewing system as actual constraint network against backdrop of other “potential” constraint networks into which it might be viably perturbed. Allows for “why” questions.

Example: organism as network of heterogeneous constraints (cont'd)

- Constraint-network picture: inspired by mainstream "local-to-global" mathematical metaphor, linked to substantial body of mathematical theory, as well as mathematical toolkits for gluing.
  - Major technical challenge: dealing with "heterogeneous" gluing.
- Corresponding modeling framework: network of partial models.
  - Representing the organism from multiple perspectives.
  - Heterogeneous partial models linked by heterogeneous constraints.
  - Two distinct constraint networks: the organism and our representation of the organism.
  - Distinctive feature of framework: allows multiple possible model / theory alternatives -- or versions -- for each "local" aspect of system organization.
- Two classes of coherence / consistency-of-fit issue.
  - Data-model compatibility. Which models are "consistent with" / "most consistent with" the data ?
  - Model-model compatibility. How to fit together the alternative local models so as to form "consistent" / "most consistent" global theories.
  - Need to develop "model calculus". But don't expect canonical, context-independent goodness-of-fit metric.

Examples: cognitive / perceptual (1)

- "Effort after meaning".
  - "Hence it is legitimate to say that all the cognitive processes which have been considered, from perceiving to thinking, are ways in which some fundamental 'effort after meaning' seeks expression. Speaking very broadly, such effort is simply the attempt to connect something that is given with something other than itself."
    - F.C. Bartlett (1932). Remembering: a study in experimental and social psychology. Cambridge University Press.

- Weak central coherence theory of autism.
  - "Faced with this bottleneck in higher-order cognition, the developing and plastic brain [of the autistic child] would likely evolve a cognitive style that avoids reliance on high level integrative processing and instead emphasizes low level features-- a pattern typical of autistic attention and perception that Frith has termed weak central coherence."
    - M.K. Belmonte et al., Autism as a disorder of neural information processing: Directions for research and targets for therapy. Molecular Neuropsychiatry (2004).

Examples: cognitive / perceptual (2)

- Body schema
  - "There are multiple reference frames in which the body is represented, so that the body schema is perhaps nothing other than the synthesis of multiple schemas by mechanisms as yet unknown. …The concept of coherence is thus central."
    - A.Berthoz (1997). Le sens du mouvement. Editions Odile Jacob. Paris.
- Attention
  - Don't construe as primarily reflecting intrinsic processing limitations. Rather, as coordinative processes maintaining coherence of purposeful action.
    - A. Allport (1993). Attention and control: Have we been asking the wrong questions ? Attention and performance XIV.
  - Coherence theory of attention. Argues that our impression of maintaining stable and detailed visual representations of the world is illusory. Instead, focused attention is allocated so as to create coherent yet unstable virtual representations.
    - R.A. Rensink (2000). The dynamic representation of scenes. Visual cognition.

Examples: neuronal / cellular (1)

The complex structure of a simple memory

Jonathan R. Wolpaw

Operant conditioning of the vertebrate H-reflex, which appears to be closely related to learning that occurs in real life, is accompanied by plasticity at multiple sites. Change occurs in the firing threshold and conduction velocity of the motoneuron, in several different synaptic terminal populations on the motoneuron, and probably in interneurons as well. Change also occurs contralaterally.The corticospinal tract probably has an essential role in producing this plasticity.While certain of these changes, such as that in the firing threshold, are likely to contribute to the rewarded behavior (primary plasticity), others might preserve previously learned behaviors (compensatory plasticity), or are simply activity-driven products of change elsewhere (reactive plasticity). As these data and those from other simple vertebrate and invertebrate models indicate, a complex pattern of plasticity appears to be the necessary and inevitable outcome of even the simplest learning.

Trends Neurosci. (1997) 20, 588–594

Examples: neuronal / cellular (2)

Orchestrating neuronal differentiation: patterns of Ca^{2+} spikes specify transmitter choice
Nicholas C. Spitzer, Cory M. Root and Laura N. Borodinsky. TINS, July 2004

- A key feature of neuronal network assembly: appropriate specification of neurotransmitters.
- Not only "genetic program". Also, activity-dependent changes in presynaptic transmitter expression.
- Leads to "matching problem": How to achieve correct match-up with postsynaptic receptors ?
- Among the complicating factors: "Field of neurons often project onto other fields of neurons with relative rather than absolute precision…"
- Multiple regulatory mechanisms: Ca^{2+} spike activity, transcription factors, protein signalling.

Examples: neuronal / cellular (3)

Speculations on the purpose of interneuron diversity

"….The diversity of interneuron types and synapses involved in recruiting and applying inhibition may therefore allow the stimulus to custom configure the location, timing and intensity of the inhibition taking place in neurons and in the microcircuit. If this customized inhibition is combined with the *in vivo* findings suggesting that the excitatory-inhibitory conductances are always balanced, then it would appear that all these parameters must be tuned and aligned relative to each other with extreme care. We have no idea yet how such an alignment of parameters could be achieved with local and/or global learning rules."

"….We therefore propose that the diversity of interneurons and their circuitry makes the microcircuit capable of processing each of a vast spectrum of different stimuli with customized specialization…."

From: Chap. 9, Interneuron Heterogeneity in Neocortex
A. Gupta, M. Toledo-Rodriguez, G. Silverberg, H. Markram
In T.K. Hensch, M.Fagiolini, eds. (2004) Excitatory-Inhibitory Balance…

Biological coherence

Tensions with the more exact sciences

Biological flexibility / variability

- A hallmark characteristic of the organism: its capacity for generating context-dependent alternative “solutions” to virtually any “problem” of internal organization or of behavior.
- An adequate theory needs not only to accommodate, but to account for, this ubiquitous phenomenon.
- Also, theory needs to confront the *sui generis* character of biological variability.
  - “Different” from variability in the physical sciences.
  - In biological contexts differences among distinct instances of an “ensemble” may carry significance, and be “actively” induced. Not merely perturbations with respect to “baseline” or “normal” system states.
  - Generation of diversity.
  - This impacts on the investigator. Can’t rely on traditional analytical approaches.

Flexibility, but not too much

Reality and immortality—neural stem cells for therapies
Jeffrey D Rothstein & Evan Y Snyder *Nature Biotechnology* **22** (2004)

How plastic should transplanted cells be?
The ability to generate neuron-restricted lines raises questions regarding what it might take to repair a dysfunctional CNS and what type of cell might require replacement. Before transplantation,what is the optimal degree of differentiation of a neural progenitor cell for a particular disease: a predifferentiated, rigidly committed state or a less differentiated and more plastic state, which would allow the cell to mature *in situ*?

Conclusions

To fully realize the therapeutic potential of neuronal progenitor cells, clinicians and neuroscientists face the following challenges: how to direct such cells (whether endogenous or exogenous) to different CNS regions to yield cells of the right type(s) and number, in the right ratio, in the right location, making the right connections with the right partners without making any wrong connections, and to shield nontargeted cells and regions from such influences. Combinations of cells may be required—various types at perhaps different developmental or differentiation stages for different phases of a given disease. If so, the answer to the question, "Which cell for which disease?", might in fact vary from disease to disease and structure to structure, to be determined empirically over the next decade.

“Mechanism” not the answer

- Accounting for this flexibility is unlikely to take the form of a canonical “mechanism” or set of mechanisms, or to be mechanism-centered.

- In fact, part of the mystery to explain is the organism’s profligacy of mechanism.
  - Capacity to generate alternative, mutually substitutable mechanisms. If one mechanism is inactivated or unavailable, another can take its place. “No phenotype” phenomenon.
  - “Same” problem may be handled by heterogeneous mechanisms, depending on locale and on context.

- Also, sidesteps question of how mechanisms are coordinated.

- Same critique applies to “control motifs”.

Example: multiplicity of mechanisms

Nature Neuroscience
July 1999 Volume 2 Number 7 pp 597 - 604

Can molecules explain long-term potentiation?

Joshua R. Sanes & Jeff W. Lichtman

Although over 100 molecules have been implicated in long-term potentiation and depression, no consensus on their underlying molecular mechanisms has emerged. Here we discuss the difficulties of providing molecular explanations for cellular neurobiological phenomena.

Neuron
Volume 44, Issue 1 , 30 September 2004

LTP and LTD
An Embarrassment of Riches

Robert C. Malenka and Mark F. Bear

Abstract

LTP and LTD, the long-term potentiation and depression of excitatory synaptic transmission, are widespread phenomena expressed at possibly every excitatory synapse in the mammalian brain. It is now clear that "LTP" and "LTD" are not unitary phenomena. Their mechanisms vary depending on the synapses and circuits in which they operate. Here we review those forms of LTP and LTD for which mechanisms have been most firmly established. Examples are provided that show how these mechanisms can contribute to experience-dependent modifications of brain function.

The unknowledge / flexibility spiral

- More significantly: How does the system deal with its own variability ?
- Helpful here to borrow economics terminology:
  - Unknowledge. Refers to intrinsic uncertainties faced by an economic actor, in particular uncertainties not reducible to a probability distribution on a pre-specifiable space of alternatives.
  - *Ex ante* / *ex post*. Emphasizes distinction between anticipated and actual resultant effects of implementing decentralized decisions made by individual agents.
- Leads to a "spiraling": Dealing with unknowledge requires flexibility, which requires variability, which leads to further unknowledge, which requires further flexibility,…
- How is it possible for the system to maintain coherence under these conditions ? In fact, relinquishing the assumption of "normal" or "baseline" system states raises question: How does the system "know" what constitutes coherence ?

“Correctness” is not the relevant notion

This suggests that processes of coherence *imposition* do not proceed via targeting of pre-determinable “correct” outcomes.

- *Ex ante* unformulability of precise “specifications” may be an intrinsic aspect of biological coherence maintenance.
- Using a cost-function or, alternately, a performance-criterion analogy: The relevant cost-functions (resp., performance-criteria) may be *ex ante* unformulable.
- To take an extreme case: The *ex ante* “world” and the *ex post* “world” may be essentially incommensurable, so that evaluative criteria for *ex post* states-of-affairs may not be expressible in *ex ante* available language.

Individuation
Achieving "appropriate" specificity

- Individuation vs. specification.
- "Unspecification-like" processes for achieving precision and specificity.
- Non-stereotyped character of the precision that results: "stereotypy -- but not quite".
  - Different instances, while very similar, are not identical copies modeled on an ideal type or template.
  - But neither should they be regarded as variants of a fixed class, or as fluctuations about some mean.
  - More strongly stated: they should not be thought of as samples drawn from some probability space.
  - Analogy: Different performances of the same musical composition.
- The distinction between specification and individuation -- and between individuals and samples drawn from a class -- is not a philosophical quibble, but impacts on important problems of biological specificity and diversity.
  - A significant source of tensions with the "more exact sciences".
  - Analogy: elliptical vs. circular planetary orbits.

Individuality: two views

Pharmacogenetics and the practice of medicine
Allen D. Roses
Nature June 15, 2000

"If it were not for the great variability among individuals medicine might as well be a science and not an art." The thoughts of Sir William Osler in 1892 reflect the view of medicine over the past 100 years. The role of physicians in making the necessary judgements about the medicines that they prescribe is often referred to as an art, reflecting the lack of objective data available to make decisions that are tailored to individual patients. Just over a hundred years later we are on the verge of being able to identify inherited differences between individuals which can predict each patient's response to a medicine. This ability will have far reaching benefits in the discovery, development and delivery of medicines. Sir William Osler, if he were alive today, would be re-considering his view of medicine as an art not a science.

From: Robert Musil, The Man Without Qualities

"…But there was something else he had on the tip of his tongue, something about mathematical problems that did not admit of any general solutions, the combination of which could bring one closer to the general solution. He might have added that he regarded the problem set by every human life as one of these…."

Exploiting the tensions: initial directions

- My belief: Proper mathematical(?) framework even for "defining" individuation not available, so begin by trying to show what individuation is *not*.
- That is, attempt to determine limitations of principle of probabilistic / statistical approaches.
  - A particular difficulty: to show that even non-stationary stochastic processes are inadequate.
  - I expect some rather speculative notions of "singular dynamics" to play a role in these "negative" investigations. Also, eventually, in the corresponding "positive" investigations.
- Along the same lines, attempt to determine limitations of principle of "local / global learning rules" as means of attaining / maintaining coherence.
- In a similar vein, explore for limitations of principle in "Milner process calculus" approaches to systems biology.
- An inherent difficulty apropos individuation:
  - No recourse to canonical (in sense of prototype) or "toy" (in sense of simplified down to essentials) models.
  - Contrasts with situation in physics, information theory.

A further source of tensions: ungraspability

- The preceding suggests that the price of adequate flexibility is "ungraspability".
  - A concomitant of self-ungraspability may be ungraspability by other entities.
  - In proper balance, this can confer selective advantage.
  - Example: virus-host interaction.
- Rather than ungraspability: non-standard modes of "grasping", "knowing", "predicting",…concordant with the non-standard modes of coherence of biological systems.
- This theme of non-standard graspability transposes to theory: For entities which exhibit non-standard modes of coherence -- notably, biological systems -- there may be limitations of principle as to what can be predicted or simulated by modeling or theorizing.
  - A basic task: to elucidate these limitations of principle, and to develop the appropriate modes of theorizing. What are legitimate targets and tests of the theory ?
  - Further complication: Biological systems - as a reflection of their plasticity - respond according to the way they are interrogated.
  - Intriguing parallel: The Internet - due to its pervasive heterogeneity and rapid change - also raises issues of limitations in simulability.
  - Also, problem of "traffic shaping. System responds as interrogated.

Supporting evidence: difficulties with synthetic biology

- Loose characterization: “Customized” design of biological circuitry.
  - “Classical” example: Industrial scale “metabolic engineering”.
  - Example: modify bacteria to overproduce endogenous or heterologous natural products.
  - Approach: Combine “rational analysis” with “directed evolution”.
  - But for actual circuit design McAdams and Arkin (2000) anticipate difficulties in practice in quantitative prediction of behavior, or even in ability to select for the specified behavior.
- Current manifestation: MIT “registry of standard biological parts”.
- Aim for predictability, reliability. In practice, surprises.
  - “You write the same software and put it into different computers, and their behavior is quite different.” -- L. You, Caltech (2006)
  - “ There is no such thing as a standard component, because even a standard component works differently depending on the environment. The expectation that you can type in a sequence and can predict what a circuit will do is far from reality and always will be.” -- F. Arnold, Caltech (2006).

Limitations of practice -- or of principle ?

- Perhaps to achieve biological modes of coherence requires biological modes of specification / imposition of specificity. But we don't know what these are !
  - Analogy: Christopher Alexander "argument" that only certain kinds of design process can yield coherent architecture; ditto for coherent software.

    -- The origins of pattern theory, IEEE Software 1999.

    Also, *The Nature of Order* (4 volumes).

- *Coherence mismatch* ?
  - Idea: Loss of coherence can occur when interconnecting or interfacing two systems having different modes of coherence (or "designed" via different modes of specificity-imposition).
  - Loss of coherence can be with respect to the coherence criteria of either -- or both -- systems.
  - Analogy: Impedance mismatch; source-channel mismatch.

Exploiting the tensions: three strategies (1)

Limitations of principle

– Try to identify "services" that the system requires, but which standard modes of coherence are incapable of providing, or providing in timely fashion.

– Alternately, try to identify "resources", e.g., information, necessary for standard modes of coherence, but which are inherently unavailable.

– Example: Shannon noisy channel coding theorem.

– Example: "A Hundred Impossibility Proofs for Distributed Computing" -- Nancy Lynch, Proc. 8th Annual ACM Symposium on Principles of Distributed Computing, 1989.

Exploiting the tensions: three strategies (2)

Coherence mismatch

- Try to bring to light differences in modes of coherence of two systems by examining the kinds of loss of coherence that result when one interconnects or interfaces the two systems.
- Example: Difficulties that an intelligent human finds in attempting to interact with an "intelligent" artifact.

  -- Lucy Suchman, "Plans and situated actions, the problem of human machine interaction", Cambridge. U. Press (1987).
- Example: Difficulties in social interaction faced by an autistic child, lacking a "theory of mind".
- Example: Brain-machine interfaces (BMI's), whereby neural activity is translated into computer and prosthetic control commands. Study of this mismatch could yield insight into nervous system modes of coherence.
- Example: Cross-species composite computer modeling. For instance, *C. elegans* and *Ascaris suum*.

Exploiting the tensions: three strategies (3)

Comparative coherence

- The idea is to transpose perspectives from one domain to another, so as to highlight similarities and differences in their respective modes of coherence maintenance. In particular, take problems that are “critical” in one domain, and see how they are resolved -- or, alternately -- totally sidestepped in the other domain.

- Example: Issues of “unknowledge” are prominent in the context of economic systems. They are also highly relevant to biological systems, but tend to be underemphasized here.

- Example: A range of performance issues arises in the design and management of communication networks. Do analogous issues -- e.g., quality-of-service issues -- arise in the context of neuronal networks ? If not, what does this tell us about nervous system coherence maintenance ?

- Classic example:von Neumann, *The computer and the brain*, 1958.