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Cells, Mechanisms and Biological Engineering

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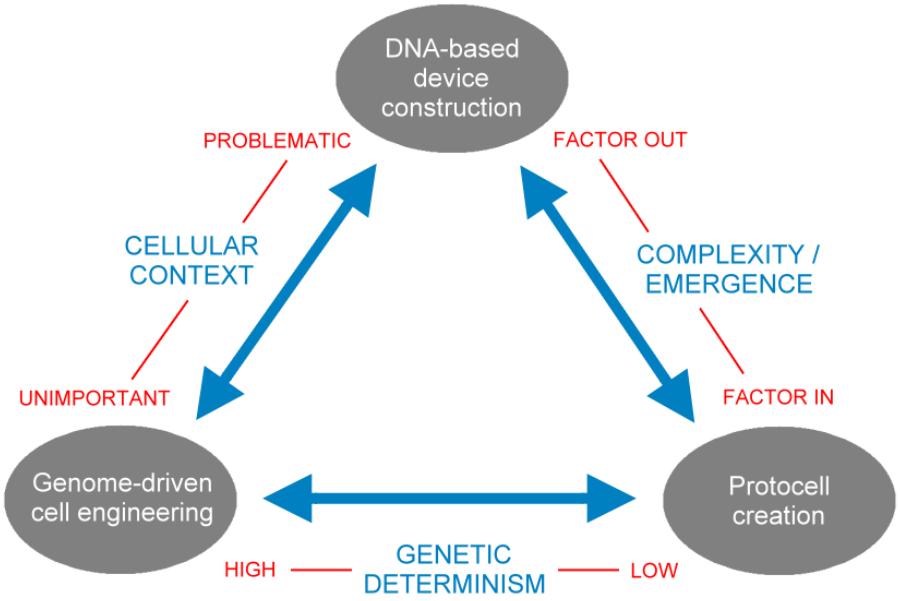
Synthetic biology

- Aim: to build novel living systems (cells / systems of cells)
- Several distinct ‘schools’:



(From O’Malley, Powell, Davies and Calvert 2007)

Synthetic biology

- Not so much a discipline as a coalition of scientists/engineers with overlapping goals / assumptions / methods
- Largely continuous with previous bio-engineering fields (genetic engineering (from 1970s), protein engineering (from 1980s))
- Distinguished by
  - the scale of its ambition
  - intensification of effort and focus
  - programmatic character
- BioBricks: re-usable ‘parts’ and ‘devices’ to implement specific functions

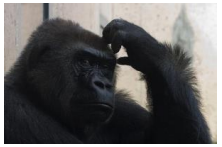
Synthetic biology

- Parallels often drawn between biological wetware and computer hardware

macromolecules	=	components
reactions	=	gates
pathways	=	circuit modules
cells	=	computers
tissues	=	networks

- Plus software / genetic information / regulatory circuit / algorithm tropes…

- How useful are such analogies?
- Biological systems are not generally stable, solid-state structures (apparent stability is dynamically achieved)
- What is the ontological status of levels in biological systems?



BioBricks and the machine stance

- The ‘machine stance’: to think of cell function as being the result of the action of macromolecular ‘machines’
  - e.g. proteasome complex; transcription complexes, etc.

- Entities have specific, structure-dependent capabilities, e.g. for molecular recognition, catalysis etc.

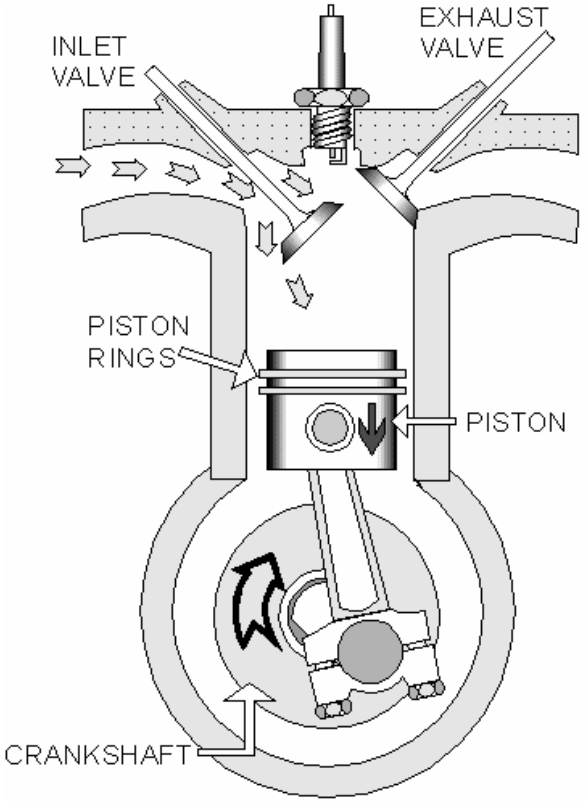
- Significant thought-shaper in molecular cell biology, nanotechnology, and MIT-style (BioBricks) synthetic biology

- Commitment to modularity / decomposability: structures and functions are aligned

- Relevant concept: mechanism

Mechanisms

- Classical conception: solid-state parts in stable relationships; relative motion defined by points, lines and planes of articulation

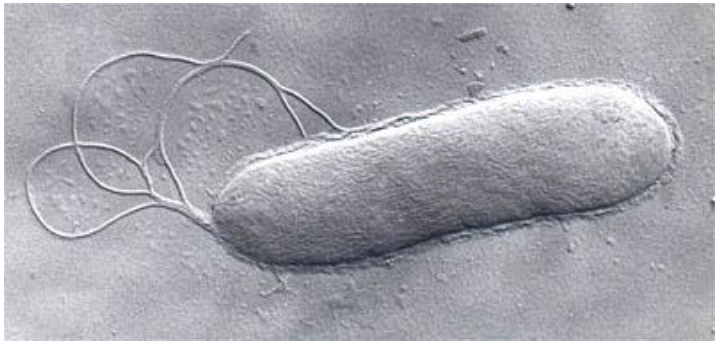


Classical mechanisms

- Key feature: physical constraints establish limited no. of degrees of freedom
- Result: mechanisms are explanatory / intelligible
  - because they lend themselves to cognitive simulation?
- Cognitive constraints on imaginability
  - Miller's Magical Number 7 (+/-2)
  - limited working memory
  - bias towards identifying causal foci and specific sequence causal events
  - 'centralized thinking' (Resnick)
  - strong bias towards simplicity (link with reductionism?)
- We can track patterns of entailment through mechanisms but struggle with complex systems – instead we often attribute emergence

Mechanisms

- But bacteria aren't clocks



- So what does mechanistic explanation mean in a biological context?

New mechanistic picture (Machamer, Darden and Craver 2000)

- Mechanisms defined in terms of entities (structures) associated with (giving rise to, supporting) activities (functions)
- Activities have set-up and termination conditions - mechanisms connect initial conditions with outcomes
- Removes the solid-state constraint; allows for interaction between mobile entities (although they don't speak in these terms)
- MDC's 'neo-mechanistic' perspective seems more readily applicable to biological systems than classical view of mechanisms

Cells

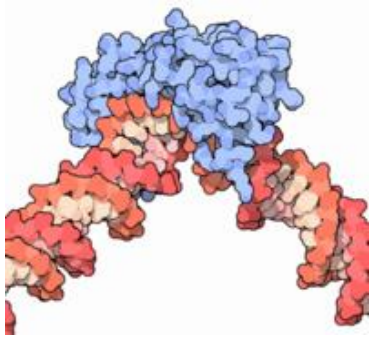
- numerous interacting entities
- apparently often supporting functions in quite a direct way
- e.g. the machinery supporting gene expression and protein synthesis, signalling, etc.

Cells

- Connection with the machine stance: the idea that structure/function relationships are straightforward

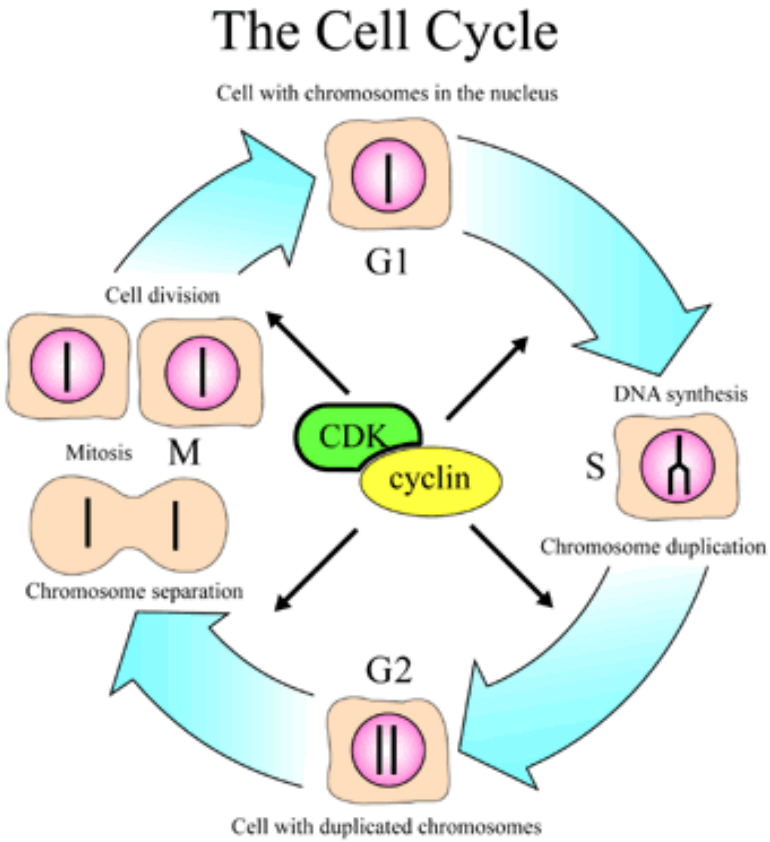
- Mechanisms can be resolved into parts that have functions that contribute towards accomplishment of the activity with which the mechanism is identified

- Can the cell be understood in these terms?



Cells

- Well we're not doing badly - consider the cell cycle:



Cell cycle

- We know about many of the most relevant entities and how / where / when they interact to drive the cycle (Nobel prizes to Hartwell, Hunt and Nurse 2001)

- Understanding is in terms of cyclins, cyclin-dependent kinases, phosphorylation/dephosphorylation events; oscillations and switching resulting from negative and positive feedback; ubiquination and targeted protein destruction, etc.

- Cell processes pictured in terms of causal constraints resulting not from collective solid-state heft but from interactional specificity of mobile entities

- Still an explanatory gap though: “The mechanisms that couple cell growth and division are poorly understood” (Morgan 2007)

Robustness and complexity

- And when we look at the robustness and complexity of cellular processes the picture becomes more involved

- Two sources of robustness (Wagner 2005):
  - (1) **Redundancy**, e.g. multiple gene copies. Knocking out one gene does not abolish the relevant function.
  - (2) **Distributed robustness**: when many different parts contribute towards a function.

- Example of distributed robustness: loss of unique (non-redundant) enzyme function need not have profound metabolic consequences. Metabolic fluxes adjust as matter is routed through alternative pathways.

- Structure / function relationships can be non-straightforward!

Biological complexity

- Entity number: high bandwidth
- Transformations via specific chemical reactions
- Self-assembly
- Fluidity
- Crowding - constraints on sampling of chemical space? (e.g. to avoid protein aggregation)
- Phase of matter weirdness / variety (meaninglessness of concept?)
- Interpenetration of levels; entanglement of processes/functions

Understanding the cell

- Physical properties of cellular milieu might be key, e.g. to timing of cellular events, oscillation rates, etc.

- Emergent phenomena can arise when agents are free to wander and interact with their environment
  - e.g. termite mound-building (Clark 1996), robotics, A-life

- Cellular fluidity is analogously conducive to emergent phenomena involving molecular machines

So are cells mechanisms?

- Not in the classical sense
- How about in the newer, state-independent (MDC) sense?
  - if we keep going with molecular cell biological analysis will it be possible to resolve molecular interactional networks into specific function-sustaining sub-networks?
  - or are some functions simply not associable with subsets of cellular sub-functions, structures or processes (holism / distributed causation)?
- At a minimum we want to identify specific entities with specific activities in order to satisfy the MDC model of mechanisms
- Grounds for doubting whether this is possible

Thinking about mechanisms

- Mechanisms are about the intersection of structure and function
- But the structures that figure in our biological explanations may be high-turnover products of far-from-equilibrium processes
- And what *is* the basis on which we individuate functions?
- Can the MDC model of mechanisms be adapted to take account of cellular complexity?

Thinking about mechanisms

- We lack reliable intuitions about cellular causality

- We need to find a way of combining aspects of the mechanistic picture with a deeper understanding of the implications of fluidity, self-assembly and other contextual constraints

Back to synthetic biology

- The factors that appear to set constraints on biology-ready concepts of mechanism look prima facie inimical to efforts to engineer cells

- There is an apparent tension and ambiguity about BioBricks-style work

- Related to its dual commitment to both the ‘machine stance’ associated with nanotechnology (structures and functions in precise alignment) and to certain computational parallels (software logic decoupled from hardware specifics) …

- … and to its ambivalence in relation to the significance of biological context versus functional modularity

On the other hand...

- Maybe systems can be conceived in terms of a specific, mechanistic (genetically specifiable?) part and a compositionally more homogeneous, bounded, environmental part that provides the relevant fluidity, boundaries, process-relevant diffusion coefficients etc.

- Protocell work in tandem with BioBricks-type creations might yield possibilities for integrating these into functioning systems with predictable properties

Conclusions?

- Current philosophical conceptions of mechanism fail to comprehend the full range of cell biological phenomena – because they depend on neat S/F alignments

- Synthetic biology will test and extend our understanding of the nature of those phenomena …

- … and perhaps help us develop a richer conception of mechanism

  (or find some other way of capturing and explicating the causal distinctiveness of cellular events and processes)

Thank you!

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