A principal limitation of virtual cell simulations using differential equation models

Motivation

The idea of building a virtual cell, i.e. the simulation of a comprehensive model of a biological cell, makes the implicit assumption that cells can be simulated.

However, the machine view of a cell or any natural system does not capture essential properties like self-organisation, which leads to certain formal requirements for virtual cell computations.

A formal model of the cell

Cells generate responses to stimuli. The series of processes and reactions involved is usually called *pathway*. More abstractly, it corresponds to a morphism (map):

$$\sigma : \Omega \quad \Gamma, \qquad \omega \mapsto \gamma = \sigma(\omega)$$

$$\Omega = \{\omega : I \quad U\} \text{ is a set of stimuli}$$
$$\Gamma = \{\gamma : I \quad Y\} \text{ is a set of responses}$$

where $I = \{t : t \quad o\}$ is a time set and U and Y are arbitrary sets (signal value spaces).

Basic cellular processes, modeled by σ, depend on the state of the system and realize *cell functions*.

$$\psi : \Gamma \quad H(\Gamma,\Omega), \qquad \gamma \mapsto \psi(\gamma) = \sigma$$

$H(\Gamma,\Omega)$ is the set of all biologically meaningful processes the cell can realize and thus a subset of Γ^{Ω}, i.e. the set of all mophisms from Ω to Γ.

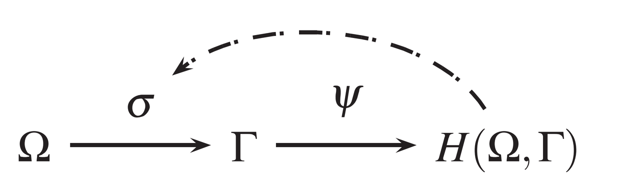
Causal entailment

Since each morphism σ associates each stimulus ω with a response γ, the question "why γ" can be answered "because ω" or "because σ".

Aristotlean analysis makes a distinction between four different fashions of causality:

Material cause: raw matter of which something is made
Formal cause: idea after which something is formed
Efficient cause: external entity/force, source of change
Final cause: goal for which something exists

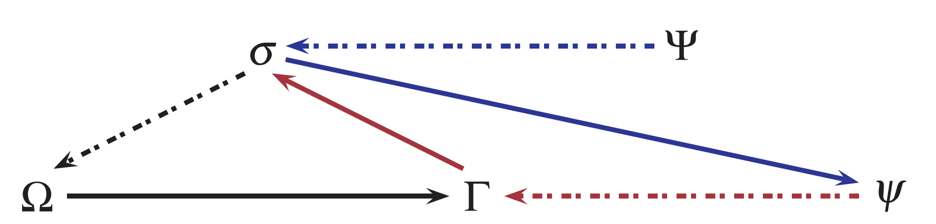
In this case, ω is the material and σ the efficient cause for γ. The efficient cause for σ is provided by the cell function map ψ.



Robert Rosen (1991) argued that there can be no "*closed path to efficient causation*" in a mechanism (in the technological sense). The mapping ψ in our abstract cell model is now indeed unentailed (with respect to efficient causation). One could now introduce a coordination map Ψ

$$\Psi : \; H(\Gamma,\Omega) \qquad H(\Gamma, H(\Gamma,\Omega)),$$

which leads to the following graph of causal entailment.



Ψ is now indeed unentailed. To avoid infinite regress, we would need to show that Ψ is entailed from within the system. The main idea here is that closure to efficient causation means that any element of a collection of things is also an image of some map.

Functional organization

Our conceptual framework now encompasses a *multi-level system*:

Coordination

$$\Psi : H(\Omega,\Gamma) \to H(\Gamma, H(\Omega,\Gamma))$$

↓

Cell Functions

$$\psi : \Gamma \to H(\Omega,\Gamma)$$

↓

Cellular Processes

$$\sigma : \Omega \to \Gamma$$

Control **Regulation** **Adaptation**

At this point, the map Ψ is still hypothetical. To show that in our abstract model it can be realized from within the system as a self-organizing process, we need to show that it is an image in some codomain within the formal system.

The mathematical framework

A *category* in the mathematical sense is the notion of abstract structures and structure-preserving operations. It consists of a class of objects, a class of morphisms between the objects and a composition operation.

A category is called *cartesian closed* if there exists the product $\Sigma \quad \Omega$ of any two objects Ω, Σ and an exponential Γ^{Ω} of any two objects Γ, Ω within the category. Then, a morphism acting on a product can be identified with a morphism acting on one of the factors,

$$\frac{\Sigma \times \Omega \xrightarrow{\tilde{\sigma}} \Gamma}{\Sigma \xrightarrow{\ulcorner\sigma\urcorner} H(\Omega,\Gamma)} \quad \downarrow\uparrow$$

where $\Sigma \quad (\Gamma^{\Omega})^{\Gamma}$.

There is an *evaluation function* $e : \Gamma^{\Omega} \; \Omega \quad \Gamma$ such that for each $\tilde{\sigma}$ there is a unique $\ulcorner\sigma\urcorner : \Sigma \quad \Gamma^{\Omega}$ fulfilling $e \circ \ulcorner\sigma\urcorner, \mathrm{id}_{\Omega} = \tilde{\sigma}$ (see also Lawvere & Rosebrugh, 2003).

Cartesian closed categories comprise morphisms that act on morphisms, which in necessary to model intracellular processes that act on other processes.

Proposition.

A model of a living cell, closed to efficient causation, corresponds to a cartesian closed category, denoted **Cell**. To ensure closure to efficient causation it is sufficient that the parametrization $\ulcorner\sigma\urcorner$ of basic cellular processes in the exponential object Γ^{Ω} has a retraction.

Theorem.

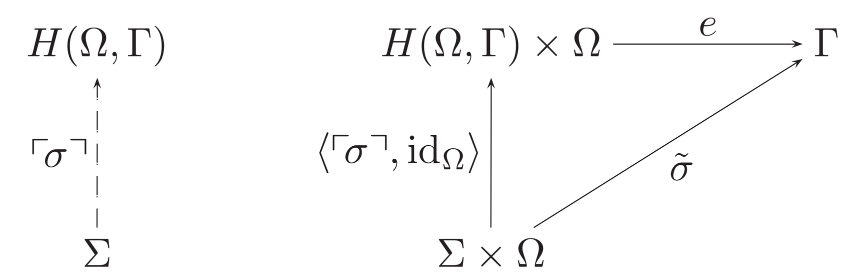
Given the mathematical model **Cell** *of a living (natural) cell, the coordination of cell functions* Ψ *is entailed from within the cell.*

Sketch of Proof.

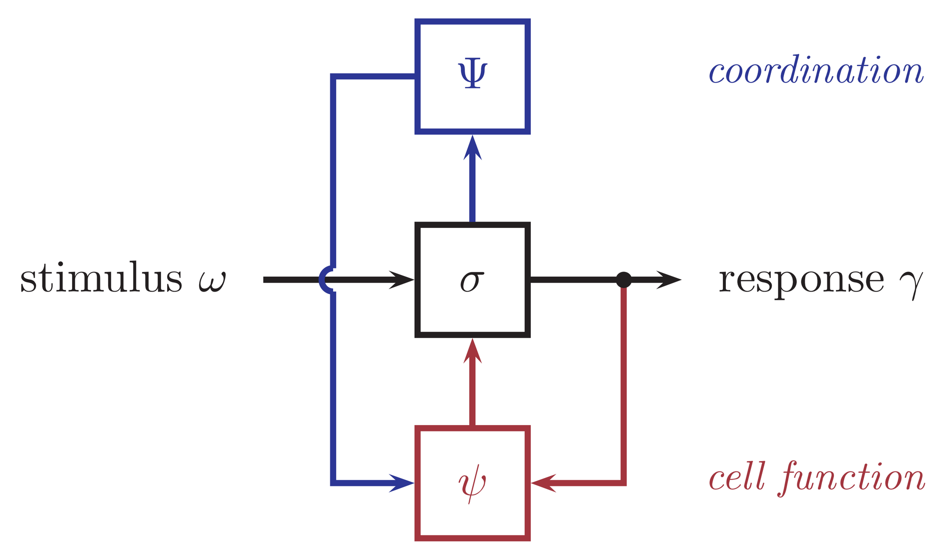
Ψ was introduced as a morphism that selects a cell function for each cellular process:

$$\Psi : H(\Gamma,\Omega) \quad \Sigma, \qquad \sigma \mapsto \psi.$$

For any object Σ and map $\tilde{\sigma} : \Sigma \; \Omega \quad \Gamma$ there is a unique map $\ulcorner\sigma\urcorner : \Sigma \quad H(\Omega,\Gamma)$ and the evaluation map $e : H(\Omega,\Gamma \; \Omega) \quad \Gamma$ for which $e \circ \ulcorner\sigma\urcorner, \mathrm{id}_{\Omega} = \tilde{\sigma}$. Note that σ is a basic cellular process while $\tilde{\sigma}$ describes a cellular process taking place in a context. This results in the following commutative diagram:



Now the retraction of $\ulcorner\sigma\urcorner$, i.e. the map $\ulcorner\sigma\urcorner : H(\Omega,\Gamma) \quad \Sigma$ for which $\ulcorner\sigma\urcorner \circ \ulcorner\sigma\urcorner = \mathrm{id}_{\Sigma}$, ensured that all maps ψ are entailed by at least one $\sigma \quad H(\Omega,\Gamma)$. Thus, it can take the role of the coordination map Ψ, which adds up to the following model of a cell governed by a self-organizing principle.



Conclusion

We have established a general abstract formal model of a cell that exists within a cartesian closed category and shares the property of closure to efficient causation with living system. The mathematical structure of Ω, Γ, or the state space in a state-space representation of dynamic systems determines whether a category is cartesian closed. The basis for nonlinear dynamic systems, encoded by differential equations, are manifolds and topological spaces, which are *not* cartesian closed.

Computer simulations based on differential equations, although able to mimic a cellular process, can therefore not capture self-organization of cell function, which is a, if not *the*, fundamental property of living systems.

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