**Definition of Biological Code**

This work critically examines the organizational principles governing living systems and introduces emerging rules that pave the way for a computational approach to understanding life. It challenges the conventional assumption. Derived from Barbieri's work, here are the general criteria for a structure or process to be considered as a biological code:

1. Two Independent Worlds: A code must connect two relatively independent "worlds" or "realms" that operate in different contexts and according to different constraints. These worlds can be physical, chemical, or informational.
2. Arbitrary Adaptors: The connection between the two worlds is established through arbitrary adaptors. "Arbitrary" here means that the relationship between the entity in one world and the one in the other is not based on physical-chemical necessity but on convention or historical accident. These adaptors are specific molecules or structures that establish the link between the sign and its meaning. E.g. the Morse code is arbitrary because alphabet keys and dot-strokes signs can be assigned to each other arbitrarily and a convention finalized their assignment. Adaptors share deep functional analogies with weak regulatory linkage in biological phenomena ([Gerhart and Kirschner, 2007](https://pmc.ncbi.nlm.nih.gov/articles/PMC1876433/)).
3. Specific Codemaker: A code must be implemented by a specific apparatus (e.g., molecular machine, or enzyme), often called the "codemaker," which is responsible for maintaining the relationship between the two worlds. The codemaker ensures the correct association between entities of world 1 and world 2
4. Establish Conventions of Associations: The code must establish conventions or rules of association between elements in two distinct ‘worlds’. These conventions are essential for the code to function as a rule-based association system. Without these specific rules, there can be no correct interpretation of the coded signals.
5. Functionally Important: The code's operation must be essential for the organism, playing a crucial role in processes such as protein synthesis, gene regulation, or signal transduction.
6. Historical Contingency: The origin and evolution of the code are often influenced by historical events or chance occurrences, leading to a specific set of rules that may not be the only possible solution but is the one that has been established over time.
7. Consistent Mapping: A crucial aspect of biological codes is that they establish consistent mappings between elements in two different biological domains. These unidirectional associations are vital for the code’s operation.

**Definition of Biological Agent**

An "agent" in biology typically refers to entities like cells or organisms that operate with some degree of autonomy. A more comprehensive list of properties that define a biological agent in this context, prioritized into primary and secondary properties ([Epstein and Axtell, 1996](https://direct.mit.edu/books/monograph/2503/Growing-Artificial-SocietiesSocial-Science-from), [Kauffman, 2023](https://academic.oup.com/book/53153), [de Castro and McShea, 2022,](https://lanzarotebiosfera.org/wp-content/uploads/2023/01/Paleobiology-a-publication-of-the-Paleontological-Society.pdf) [Prigogine, 1980](https://www.amazon.de/-/en/Being-Becoming-Complexity-Physical-Sciences/dp/0716711087)) reads as:

Principal properties:

1. Autonomy: The ability to act independently based on internal processes and external stimuli, without constant direct control or intervention from external entities.
2. Self-Organization: The capacity of open systems to achieve stability far away from equilibrium, typical of dissipative structures ([Prigogine, 1969](https://www.scirp.org/reference/referencespapers?referenceid=1336803)).
3. Rule-Based Behavior: Follows rules that govern its actions, such as metabolic pathways or developmental processes.
4. Task Accomplishment: Carries out goal-oriented functions that serve its survival and reproduction, such as nutrient uptake, reproduction, or response to stimuli.
5. Adaptability: Ability to adjust behavior or structure in response to environmental changes.

Secondary properties:

1. Complexity: Exhibits emergent behaviors or structures that arise from simpler components and cannot be predicted as the simple sum of the properties of those simpler components.
2. Interactivity: Engages in interactions with other biological agents or components of its environment.
3. Homeostasis: Maintains internal stability despite changes in external conditions.
4. Autopoiesis/Reproduction: Capable of producing self-similar offspring or replicating itself.
5. Inheritance: Traits and properties are transmitted to offspring.
6. Evolutionary Potential: Traits can evolve over time through genetic or phenotypical changes.

Agents can be described as entities that interact with their environment and other agents according to the primary properties discussed earlier. True biological autonomy requires that an organism can "actively maintain its identity: for example, by modulating its internal, constitutive organization, in accordance with environmental changes" ([Moreno and Mossio, 2015](https://www.scirp.org/reference/referencespapers?referenceid=2673503)). This goes beyond mere persistence to include active self-maintenance (secondary properties). The topic of autonomy is amply discussed and broken down in the Technological Approach to Mind Everywhere (TAME) framework from Michael Levin ([Levin, 2022](https://www.frontiersin.org/journals/systems-neuroscience/articles/10.3389/fnsys.2022.768201/full)). Rather than requiring absolute self-maintenance, TAME frames autonomy as graded competency in preserving identity through goal-directed plasticity, where even simple systems (like regenerating planaria or synthetic biohybrids) qualify as agents based on their ability to adaptively modulate organization across scales.   
We adopt this perspective to define what a biological agent is, because it maps the autonomy property into a graded axis of goal-oriented competency and makes biological agents more treatable in terms of ABM simulations ([Eberlen et al, 2017](https://rips-irsp.com/articles/10.5334/irsp.115)). According to TAME, for example, proteins could not be considered bioagents, because they lack two key features: 1. anticipatory regulation via internal models, specifically Test-Operate-Exit (TOE) loops in allostatic regulation, and 2. the ability to scale their agency across biological levels, meaning they cannot adjust their goals to address challenges at higher organizational levels.

However, despite not qualifying as proper bioagents, proteins’ behavior can still be modeled by using ABM ([Maestri et al, 2022](https://www.nature.com/articles/s41598-021-04205-8)). This approach allows for the pragmatic use of ABM techniques while maintaining theoretical consistency with the TAME-based definition of biological agency, adopting the distinction between biological agency and computational representations of sub-agents' observable phenomena (via ABM simulations, see the next section titled Definition of agent based modelling).

**Definition of agent based modelling (ABM**)

Agent-Based Modeling (ABM) is a computational simulation technique that investigates complex systems by modeling autonomous, interacting entities (agents) within a defined environment. These agents follow predefined rules, leading to emergent system-level behaviors that cannot be deduced from individual agent behaviors alone ([[Smythos: ABM]](https://smythos.com/ai-agents/ai-tutorials/agent-based-modeling-definition/)). ABM adopts a bottom-up approach, where macro-scale patterns arise from micro-scale agent interactions ([deSmith et al, 2024](https://www.spatialanalysisonline.com/HTML/agents_and_agent-based_models.htm), [Eberlen et al, 2017,](https://rips-irsp.com/articles/10.5334/irsp.115) [Bonobeau, 2002](https://pmc.ncbi.nlm.nih.gov/articles/PMC128598/)). TAME theory suggests ABMs could better approximate biological agents by incorporating: 1. Graded autonomy metrics (persuadability scores, goal complexity), 2. Multi-scale goal hierarchies (e.g., organelle priorities influencing cell behavior), 3. Bio-inspired credit assignment (reinforcement signals shaping future decisions).

Core requirements:

1. Agent Autonomy: Agents operate independently based on internal rules, without centralized control. They exhibit: a. Self-directed behavior: Decision-making based on local information, and b. Social interaction: Protocols for communication with other agents (e.g., message-passing in crowd simulations)
2. Heterogeneity: Agents possess unique attributes, behaviors, or decision-making algorithms
3. Environment: A structured space (physical or abstract) where agents act and interact.
4. Interaction Rules: Explicit protocols governing agent-agent and agent-environment dynamics (reactive or goal-oriented)
5. Emergence: System-wide patterns arising from agent interactions
6. Adaptability: Agents may learn or evolve via Reinforcement Learning ([Singh, 2024](https://builtin.com/articles/agent-based-modeling)) or memory-driven behavioral updates ([Bonobeau, 2002](https://pmc.ncbi.nlm.nih.gov/articles/PMC128598/))

Limitations:  
Current ABMs remain approximations: they simulate agency but lack, as of now, the self-organizing, open-ended plasticity of living systems.

|  |  |  |
| --- | --- | --- |
| Aspect | ABM Agents | Biological Agents |
| Autonomy | Rule-bound (no true agency) | Goal-directed plasticity |
| Adaptation | Limited to pre-coded scenarios | Open-ended learning/innovation |
| Scale Integration | Flat hierarchy (no sub-agents) | Nested agency (cells → tissues → organisms) |
| Teleology | Designer-assigned purpose | Intrinsic self-preservation goals |

**Table A.1.** Crucial Differences of ABM vs biology agents

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