Interfacing Synthetic Cells with Biological Cells: An Application of the Synthetic Method

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Abstract

The "synthetic method" is the methodological approach that guides current scientific attempts of understanding natural processes by the construction of hardware, software, and/or wetware models from scracth. It focuses the scientific inquiry on the generative mechanisms of the target processes, with the goal of testing and improving scientific hypotheses about them.
This article presents an application of the synthetic method based on cutting-edge technology: the construction of "synthetic cells" (also known as "artificial cells") capable of exchanging chemical signals (and, in this sense, of 'communicating') with biological cells.

The Synthetic Method

The "synthetic method" (SM) is the methodological strategy through which the sciences of the artificial intend to overcome merely engineering purposes, and positively contribute to the scientific exploration of natural processes – biological and cognitive processes *in primis* (Damiano et al., 2011). The adjective "synthetic" defines the peculiarity of this method. It emphasizes the programmatic divergence of the SM from the traditionally privileged direction of the scientific exploration – i.e., analysis. The specificity of the SM is that it proposes to study natural processes not by dissecting natural systems into their parts, but by (re-)constructing these systems from scratch, based on available scientific knowledge. It promotes a form of scientific research that focuses not on the components of biological and congitive systems, but on the relationships that coordinates these components in integrated units – the systems. This "constructive" or "syntethic" approach is often associated by contemporary research to a methodological slogan – "understanding by building" (Pfeifer and Scheier, 1999) – that concisely defines the related scientific practice. That is: the construction and experimental manipulation of artifacts that reproduce target natural process on the basis of scientific hypotheses, and thus can be considered as "material models" of these processes, useful to experimentally test the hypotheses they express.
The SM was elaborated, between the 1910s and 1940s, by early lines of (Proto-)Cybernetics, which built mainly "hardware" (robotic) models of cognitive and biological processes. In the middle 1950s, with the emrgence of classical AI, the focus moved to "software" (computational) models of biological and cognitive processes, which, in the 80s, became the main research tool of the arising Artificial Life. Lately, with the development of Synthetic Biology (SB), the SM is implemented also through "wetware" (chemical) models of biological and cognitive processes.
Here we present an application of the SM in SB that has the potentiality of opening a new way of experimentally exploring life and cognition. The wetware models presented in this paper can be defined as "interactive models" (Damiano et al., 2011), since they do not simply reproduce the processes under inquiry, but also engage natural systems in dynamics that could be of scientific interest.

Synthetic Cells that 'Communicate' with Biological Cells

SB is a discipline that combines engineering and biology, and aims at designing, constructing and assembling biological components that do not exist in nature. Bottom-up/cell-free/chemical SB is a branch of SB referring to those studies based on the assembly of biological systems from scratch.
One of the bottom-up SB projects aims at assembling synthetic cells (SCs) of minimal complexity (Luisi, 2002). The construction of such structures can be informative to retrace the origin of life on Earth, or for developing new tools for nano-bio-technology (e.g., assays, diagnostics, tools for biochemistry/molecular biology/cellular biology, advanced drug delivery systems, nanomedicine, nanorobotics).
An increasing number of recent reports shows that current technology already permits the construction of SCs of sufficient complexity that can play a role in biotechnology. In particular, the state-of-the art is based on the fusion between liposome technology and cell-free protein synthesis. SCs, as biological cells, can produce different types of proteins, such as polymerase, synthases, pores, cytoskeletal ones. Interestingly, the protein production can occur in controlled manner, and therefore SCs become somehow "programmable" – thanks to the use of genetic regulation mechanisms. The latter aspect is very important, because it allows the design and the construction of SCs which "respond" to chemical stimuli.
We and others have devised the possibility of constructing SCs capable of exchanging chemical signals with natural cells or with other synthetic cells. Actually, this topic was already present as a general concept in previous papers (discussed in Stano et al., 2012), but, with just one exception (Gardner et al, 2009), experimental approaches were missing.

After some years of technical progresses, we count now on a small number of pioneer papers that have demonstrated the possibility of interfacing simple SCs with biological cells (bacteria), and even with other SCs (Adamala et al., 2017; Tang et al., 2018). Most examples refer to unidirectional communication (Lentini et al., 2014; Adamala et al., 2017; Tang et al., 2018; Rampioni et al., 2018), but there is also one example of SCs-bacteria bi-directional communication (Lentini et al., 2017) where the two communication partners established an ordered sequence of actions.

Our recent contribution – here shortly described – has been focused on the unidirectional communication between synthetic cells and a pathogenic bacterium, *Pseudomonas aeruginosa*, based on the quorum sensing molecule C4-HSL (Rampioni et al., 2014, 2018). We firstly design SCs and tested their capabilities with numerical models, then these cell-like structures were assembled in the laboratory by an efficient procedure, and their capability of sending a chemical signal to *P. aeruginosa* was successfully tested (Figure 1).

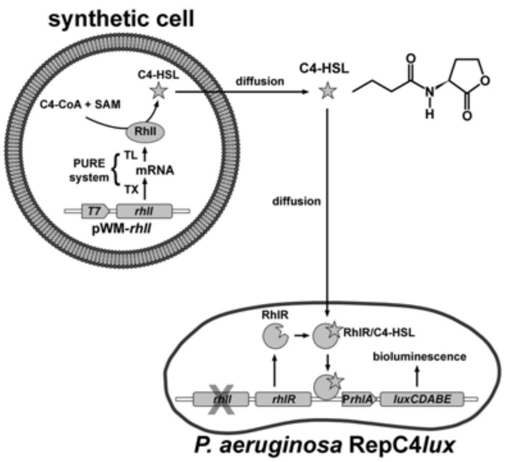

Figure 1. SCs synthesize in their aqueous lumen an enzyme (RhlI) by gene expression. RhlI synthesizes the signal molecule C4-HSL from two precursors. C4-HSL is a small compound that can freely escape from SCs and reach *P. aeruginosa* cells by diffusion in the aqueous environment. In these bacteria, C4-HSL activates an easy-to-measure bioluminescence response, witnessing a successful sense-and-activate genetic mechanism. The other experimental systems mentioned in the text operate according to similar principles. Reproduced from Rampioni et al., 2018, with permission of the Royal Society of Chemistry.

Relevance

In the synthetic exploration of life and cognition, the goal is generally twofold. Firstly, with the SM we intend to improve current hypotheses on the mechanisms underlying the target processes. Indeed, the SM allows to test these hypotheses, and providing feedback on them, based on the experimental exploration of (hardware, software, and/or wetware) synthetic models of the target processes. Secondly, with the SM we can use scientific hypotheses on the mechanisms underlying biological and cognitive processes to build better computational and/or engineering artifacts, able to exploit these mechanisms to enhance their performances.

The wetware artifacts presented in this article potentially offer advancements in both these directions. With regard to scientific research, they pave the way to synthetic studies on communicative coupling between natural cells, and could be relevant for the development of radically embodied theories of intersubjective and collective cognition (Damiano and Stano, 2018). Indeed, these artifacts are not “merely imitiative” models of cellular communication, and can be considered as “phenomenologically interactive models” (Damiano et al., 2011). Although they are not fully based on plausible mechanisms for cellular communication, and thus simply imitate cellular communication, they can engage biological cells in communicative dynamics, and be used as tools to experimentally explore communicative and collective behaviors in natural cells. With regard to technological applications, interfacing SCs to biological cells is highly relevant, as it will lead to next-generation vectors for nanomedicine (i.e., intelligent systems capable of interrogating their biological environment and behave accordingly). Moreover, programmable SC/SC chemical communication will pave the way to design of high-order multicellular synthetic systems.

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