Cells Are Integrated Multiprocessing Analog Computing Devices—Part 1

Royal Truman[1]*, Amit Singh[2], and Peter Borger[3]

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[1] University of Konstanz, Konstanz, Germany
[2] Institute for Biomechanics, ETH Zurich, Switzerland
[3] peter.borger@wort-und-wissen.de
* Correspondence: royal.truman@uni-konstanz.de

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Abstract

A computational model of biological cells is presented, conceptualizing them as networks of thousands of coordinated *analog* computing programs, orchestrated by sensors responsive to environmental cues, particularly chemical concentration gradients. These cellular sensors function as dynamic biological variables, performing decision-making to modulate biochemical processes across a continuum of states. By interpreting cells as information-processing systems, this model elucidates their core behaviors, overcoming the formidable complexity of underlying physicochemical interactions.

Simple Summary

This research paper argues that biological cells are best understood as sophisticated analog computing devices rather than just a collection of chemical reactions. The authors propose a top-down framework, where thousands of cellular sensors act as programming variables, detecting concentration gradients to make logical decisions. Unlike digital systems, these analog processes use continuous physical quantities to regulate essential functions like growth, repair, and reproduction. By interpreting biochemical interactions as logic-processing events, the study provides a unifying model for the complex engineering found in nature. This approach highlights how cells integrate hardware and software to achieve autonomous, purposeful behavior across generations.

Introduction

Cells are the fundamental unit of life, capable of autonomous reproduction, energy production, growth, adaptation, self-protection, self-repair, and recycling. Despite the vast amount of research on how individual cells function and are assembled into organisms, a comprehensive, holistic understanding seems more elusive than ever (Minelli, 2021; Mukherjee, 2022; Ball, 2023; Martinez, 2023).

The origin-of-life (OoL) community insists that only material processes must explain everything. The consequence is that allegedly prebiotic self-sustaining chemical reactions must have eventually led to cellular life (Eigen and Schuster, 1979). However, speculating about a multitude of fictitious abiotic individual chemical reactions ignores the fundamental essence of cells, which is what needs explaining. They are capable of autonomous growth, adaptation, self-protection, self-repair, recycling, and producing both their own chemical components and usable energy. Cells coordinate all these processes as recognizable, holistic entities, and reproduce with their individual processes and components in a continuously functional state, reliably for countless generations.

Cells possess the special ability to regulate biochemical processes, as dis-

cussed in Appendix 1. But a collection of chemical reactions will not bootstrap into a functional cell.

In this 3-part series, we offer an overarching interpretation of cells as self-contained information processors. Understanding the logic-processing aspects provides a top-down, unifying systems approach, relegating the endless chemical details as 'merely' implementation details.

Various computational models have been applied to describe how cells interact and organize their processing activities internally. For example, concepts from distributed computing and communication mechanisms between the processors have been used to design distributed cellular network models (Goñi-Moreno et al., 2013; Moškon et al., 2021). In addition, various agent-based models (ABMs) have been used to model interactions between cells, organoids, tissues, and bacterial communities, helping to identify emergent system behavior (Pleyer and Fleck, 2023).

These views provide valuable insights into the design and architecture of cellular computing, but we believe a key insight needs to be established. In a nutshell, we believe cells consist of thousands of kinds of analog computing devices, designed to solve distinct problems while collaborating to achieve higher-level goals. Fundamentally, decisions are computed at sensors that are then implemented by recruiting and assembling the necessary *molecular machine* 'hardware' on-demand. Cells disassemble the hardware once they are no longer needed. Through careful regulation, the copies of analog processors can range from none to millions, working in parallel.

Our goal in this 3-part series is to provide a top-down conceptual framework to make sense out of the tens of thousands of cellular processes found throughout nature.

What Are Analog Computing Devices

We offer the following definition of a human-designed analog computing device.

> "Analog computing devices model problems by using continuously changeable physical quantities, like electrical, mechanical, or hydraulic properties, to represent corresponding continuous values. Unlike digital computers that use discrete numerical values, the physical construction of analog computers allows changes in a variable X to directly and continuously produce the intended corresponding function of that variable, $f(X)$."

Ancient examples include sundials, water clocks, candle clocks, the Antikythera mechanism, and astrolabes (Ulmann, 2022). For centuries, slide rules were state-of-the-art computational devices. Current examples include mechanical watches and industrial automated control devices. Future technologies being developed include quantum analog computers using quantum states as continuous variables, neuromorphic computing, and optical analog computers based on intensity, phase, and polarization of light as variables.

The concept of analog computing devices is illustrated by the examples shown in Figure 1.

Real-time analog computing can perform abstract calculations and can control processes.

Cellular Processes Are Regulated by Concentration Gradients

The continuous, analog nature of cellular logic is observed in most, if not all, regulated processes. Some examples are provided in Table I, where concentration gradients produce a rheology-like output. By *signals*, we mean any stimulus interpreted by cellular sensors, such as photons, pressure, temperature, protons, electrons, and so on.

Complex multistep cellular processes are up- and down-regulated using dedicated sensors, as illustrated in the examples in Table II.

Key Role Played by Sensors

An important insight revealed by the examples in Figure 1 is that there is a sensing element, i.e., a precisely crafted interface able to recognize input values and connect them to the rest of the processing system. Human technologies use many kinds of sensors, such as those mentioned in Table III, to regulate equipment. Part of the sensors serve as housings to contain or organize the sensing core element, ensuring that they function effectively. This detail will help clarify how cellular sensors function.

Figure 2 illustrates the key concept of analog computing: a physical-mechanical process transforms a continuous input into an informative continuous output.

Calibrated Interplay of Sensors and Concentration Gradients

Researchers often study how chemical interactions occur, for example, at cell surface binding sites, nuclear receptors, and enzyme active sites to *understand how a cell works*. The assumption is that cellular processes are fundamentally mere chemistry. We view these interactions as engineering details to achieve cellular purposes. Focusing on the fine details instead of the architectural system is unlikely to elucidate very much about how cells function.

The interaction of signals with the relevant sensor is ensured through judicious combinations of biochemicals such as nucleotides and amino acids, plus often ligand attachments

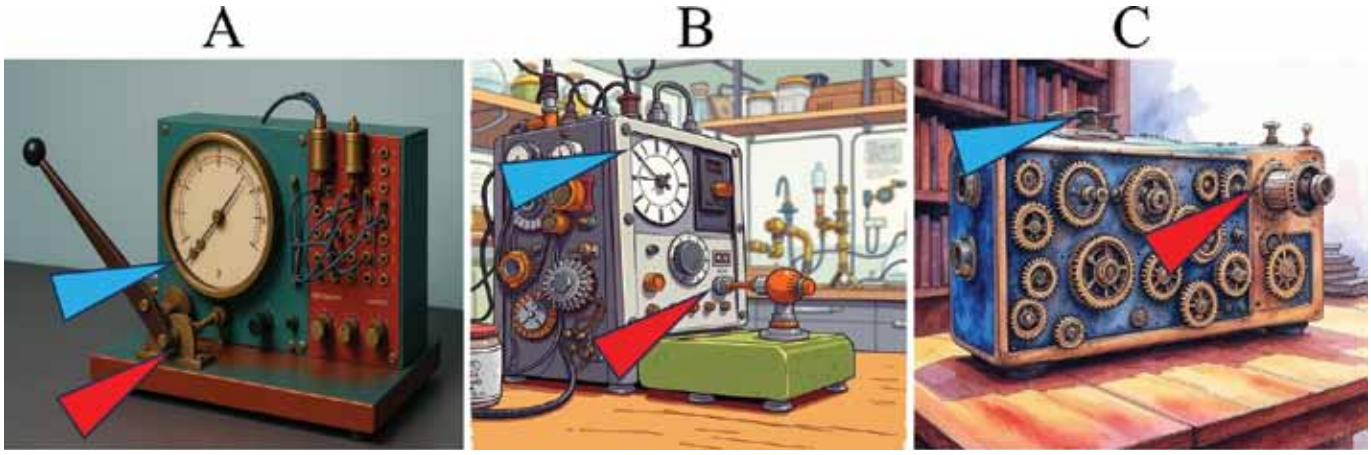

Figure 1. Analog computers convert continuous input values into a corresponding output function using carefully engineered mechanical components. The red arrows point to where input values (signals) are sensed and where conversion to the output function is initiated. The blue arrows point to where the continuous outcome occurs or is displayed. Conceptual images generated by AI.

to produce distinctive 3-dimensional recognition features. Chemical modifications are often used for this purpose. In fact, about 137 kinds of enzymatic chemical modifications have been identified on human RNAs alone, regulated according to cell type and other conditions (Modomics, 2024). Errors in these modifications cause serious problems, generally resulting in diseases (Li and Mason, 2014). For instance, around 27 kinds of chemical

Table I. Signaling gradients produce a continuum of outcomes.

Signaling effector	Description	References
Transcription factors	Control the rate at which a Preinitiation complex (PIC) is formed at promoters.	Petrenko et al., 2019; Farnung and Vos, 2022; Naqvi et al., 2023; Portillo-Ledesma et al., 2024
Transcription factors	Control the rate of polymerase assembly at enhancers.	Martinez-Ara et al., 2023; Domingo et al., 2024; Zhang et al., 2024
Glucose	Control the rates of cellular metabolism or growth.	Carey et al., 2013; Han et al., 2016;
Oxygen	Control the activity of hypoxia-inducible factors (HIFs). (Specific genes are activated).	Ziello et al., 2007; Nguyen et al., 2013
cAMP	Control the rate of activation of several genes.	Walia et al., 2016; Chakraborty et al., 2022
Ca^{2+}	Control the activity of Calcium-dependent enzymes in neurons, such as CaMKs.	Rosenberg and Spitzer, 2011; Mohanan et al., 2022; Virdi et al., 2022
miRNA	Inhibit mRNA translation.	Biasini et al., 2021; Kilikevicius et al., 2022; Ning et al., 2023
Splicing factors	Control selection of alternative splicing (leading to different isoforms).	Li et al., 2021; Ding, 2022; Snyman and Sen, 2023
RNA-binding proteins	Stabilize or destabilize mRNAs, influencing their half-life.	Modic et al., 2024; Komori et al., 2025
Mechanical forces	Sensed by integrins and other mechanosensors, translating into biochemical signals.	Di et al., 2023
Mechanical strain	Regulates nuclear localization of YAP/TAZ proteins.	Koushki et al., 2023; Kim et al., 2024

Table II. Cellular processes respond along a continuum of values.

Process	Processing steps	References
Signal Transduction Pathways	***Protein Kinase Cascades*** Kinases like MAPK (Mitogen-Activated Protein Kinase) are activated in a graded manner depending on the strength and duration of the signal.	MacKeigan et al., 2005; Yoe and López, 2020
	G-Protein Coupled Receptors (GPCRs) Ligand binding to GPCRs leads to a graded activation of downstream effectors, such as adenylate cyclase or phospholipase C.	Powers et al., 2024; Seger, 2024
	Calcium Signaling Intracellular calcium levels regulate various processes, including muscle contraction and neurotransmitter release, in an analog fashion.	Nanou et al., 2016; Kolodkin-Gal et al., 2023; Oh, 2023
Metabolic Pathways	***Enzyme Substrate Interactions*** Enzymes catalyze reactions at rates proportional to substrate concentration until saturation is reached.	Choi et al., 2017; Yu et al., 2023; Olmeda and Rulands, 2024
	Feedback Inhibition Metabolic pathways often involve feedback loops where high concentrations of end products inhibit upstream enzymes, modulating pathway activity continuously.	Liu and Birsoy, 2023; Wang et al., 2024
	Allosteric Regulation Allosteric effectors can modulate enzyme activity in a graded manner by changing their conformation.	Anderson et al., 2024; Tee and Lim, 2024
Cell Cycle Control	***Cyclin-Dependent Kinases (CDKs)*** CDK activity is regulated by the concentration of cyclins, which rise and fall during different phases of the cell cycle.	Ford et al., 2023; Pellarin et al., 2025
	Checkpoints Cell cycle checkpoints respond to varying levels of damage signals, allowing for variable delays depending on the severity of the insult.	Solier et al., 2012; Li et al., 2023
Protein Degradation	***Ubiquitin-Proteasome System*** The rate of protein degradation depends on the concentration of ubiquitin ligases and substrates.	Wang et al., 2023; Soh et al., 2024
	Autophagy Autophagic flux is modulated by nutrient availability and stress signals in a graded manner.	Chimenti et al., 2022; Perucho-Jaimes et al., 2024
Membrane Potential and Ion Channels	***Voltage-Gated Ion Channels*** Membrane potential changes influence ion channel opening probabilities in a continuous fashion.	Chang et al., 2023; Sakellakis et al., 2024;
	Action Potentials While action potentials themselves are digital, the underlying ion flow through channels is an analog process influenced by voltage gradients.	Brunner and Szabadics, 2016; Sakellakis et al., 2024

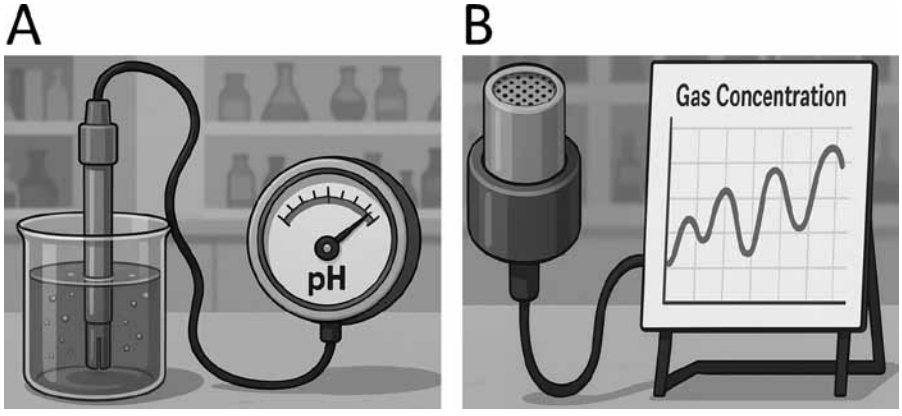

Figure 2 *(left)*. In analog computing, a physical-mechanical process transforms a continuous input into a continuous informative output. A. A sensor identifies the concentration of a substance in a liquid, such as protons, and communicates this along a continuous response. B. Here, the concentration of a gas is mechanically determined and transformed along a continuous scale. Illustrative examples only, generated by AI.

Table II *(continued)*. Cellular processes respond along a continuum of values.

Process	Processing steps	References
Synaptic Transmission	***Neurotransmitter Release*** The amount of neurotransmitter released depends on the frequency and intensity of presynaptic action potentials.	Zbili et al., 2016; Ralowicz et al., 2024
	Receptor Desensitization Receptors can become desensitized in a concentration-dependent manner, affecting synaptic strength.	Field et al., 2021; Stockwell et al., 2024
Chromatin Dynamics	***Histone Modification*** The degree of histone acetylation, methylation, or phosphorylation influences chromatin accessibility and gene expression in a graded manner.	Liu et al., 2023; Bu et al., 2025
	DNA Methylation Levels of DNA methylation can vary across regions, influencing transcriptional activity in a graded manner.	Jin and Robertson, 2011; Héberlé and Bardet, 2019
Oscillatory Systems	***Circadian Rhythms*** Circadian clocks rely on continuous oscillations of protein levels and activities that are modulated by environmental cues.	Liu et al., 2024; Nishio et al., 2024
	p53-Mdm2 Oscillations The p53 tumor suppressor protein exhibits oscillatory behavior in response to DNA damage, with amplitude and frequency reflecting the severity of damage.	Geva-Zatorsky et al., 2006; Proctor and Gray, 2008
Stress Response Pathways	***Heat Shock Proteins (HSPs)*** HSP induction occurs in response to temperature increases, with higher temperatures leading to greater induction.	Tomanek, 2010; Lewis et al., 2016
	Unfolded Protein Response (UPR) UPR signaling adjusts according to the level of unfolded proteins in the ER, enabling graded responses to stress.	Chen et al., 2024; He et al., 2024
Developmental Gradients	***Morphogen Gradients*** Morphogens like Sonic Hedgehog (Shh) or BMPs establish concentration gradients that specify cell fates in a position-dependent manner.	Greenfeld et al., 2021; Simsek and Özbudak, 2022
	Wnt Signaling Wnt ligands induce graded responses that determine tissue patterning during development.	Green et al., 2020; Pond et al., 2020
Immune System Responses	***Cytokine Signaling*** Cytokine concentrations dictate the strength and type of immune response, allowing for fine-tuned regulation.	Altan-Bonnet and Mukherjee, 2019; Cui et al., 2024
	T-Cell Activation T-cell receptor engagement triggers analog-like responses based on the affinity and duration of interaction with antigens.	Zhong et al., 2013; Wu et al., 2023

modifications are necessary for tRNAs to be recognized by mRNA codons (Kirchner, 2015; Lorenz, 2017; Agris et al., 2018; Cappannini et al., 2024).

When considering sensors, it is useful to distinguish between the core sensing element and the housing used to ensure proper functioning. Some chemical details in cellular sensors can be defined as the sensing and logic processing part, whereas other parts are only supportive infrastructure. The latter can often be neglected in order to understand the logic processing being carried out.

Only Portions of Cellular Sensors Specify Intended Binding Partners

Cellular sensors recognize three-dimensional features. For example, codon-anticodon interactions involve primarily only two or three H-bonds from each nucleotide binding partner. Most of the tRNA molecule and ribosome 'merely' fine-tune the microenvironment to optimize the bonding geometry. Each codon defines adjacent sensors on the mRNA strand, thereby specifying where each is located. These precise engineering details are necessary to avoid interacting with the far more numerous identical but incorrect nucleotide triplets distributed among all RNA, as discussed in Appendix 2.

Binding locations can be fine-tuned to regulate their responsiveness. These refinements are accomplished by

Table III. Examples of human-designed sensors.

Sensor	Input → output	Description of technology
Photometer	Light intensity → electrical signal	Intensity of light transmitted through a solution responds gradually to the concentration of a dissolved substance. This allows the concentration of substances to be calculated using the Beer-Lambert law.
pH Meter	Electrical potential → analog pH value	Electrical potential difference across a glass electrode responds gradually with proton concentration, enabling a pH value to be computed.
Thermometer	Temperature → volume change	Volume changes in mercury allow temperatures to be measured.
Pressure meter	Mechanical deformation → electrical signal	Deformation caused in a membrane is detected to determine the pressure of gases.
Flow meter	Pressure difference or velocity → flow rate	Changes in pressure, velocity, or other parameters are detected to determine volume or mass flow rates.
Optical meter	Light presence, reflection, or interruption → electrical signal	Light rays are converted into electrical signals to detect the presence or absence of objects or of their movement.
Electrochemical meter	Redox reaction current or voltage → current/voltage proportional to concentration	Oxidation-reduction reactions are used to measure, for example, gas concentrations.
Wind meter	Wind force → electrical signal	Propeller rotation or ultrasonic time differences are detected to determine wind speed and direction.
Hydrometer	Buoyancy force / sinking depth → density reading (via calibrated scale)	The depth a hydrometer sinks allows a liquid's density to be determined.
Oscilloscope	Voltage over time → visual display (graph on screen)	Voltage changes over time are visualized, allowing users to interpret signals from sensors in medical, automotive, and electronic diagnostics. This is achieved by continuously performing analog mathematical operations, such as addition and subtraction of input signals.

modifying the surrounding region by attaching specific ligands, by using double-strand base-pairing along parts of RNA, by using cysteine-cysteine bonding in proteins, and by other techniques. Sometimes binding interactions represent the normal operation of a sensor, and other times, these only play a supportive role.

- Histone proteins are modified by enzymes that add methyl groups to specific lysine residues, such as H3K4 or H3K27, to regulate gene transcription. For example, trimethylation of H3K4 (H3K4me3) promotes transcription, while trimethylation of H3K27 (H3K27me3) represses it (Ruthenburg et al., 2007). The lysine residues and their surrounding regions act as sensors (recognition sites) for methyltransferases, enabling precise targeting of these modifications.
- Glycosylation modifies proteins for various purposes. For example, O-linked glycosylation at serine or threonine residues can serve as a signal for sorting proteins to specific cellular compartments, such as the lysosome or Golgi apparatus (González, Brito, and González, 2012). Additionally, glycosylation, particularly N-linked, enhances protein solubility and promotes proper folding in the endoplasmic reticulum. Here, specific serine and threonine residues with their surrounding regions act as sensors.
- Phosphorylation often occurs in signal transduction, where serine, threonine, or tyrosine residues and their surrounding region act as sensors. These trigger kinases (called 'writers') to add phosphate groups, while phosphatases (called 'erasers') remove these groups (Han et al., 2017).
- Small regions of transcription factors (TFs) bind to DNA cis-regulatory elements, which act like sensors. Chemical modifications, such as TF phosphorylation or DNA methylation, can alter the affinity or specificity of these binding events (Glasgow, 2021).

It is noteworthy that cellular sensors are assembled when and where needed, in the proper copy number.

Some cellular sensors are designed to interact with different signal mol-

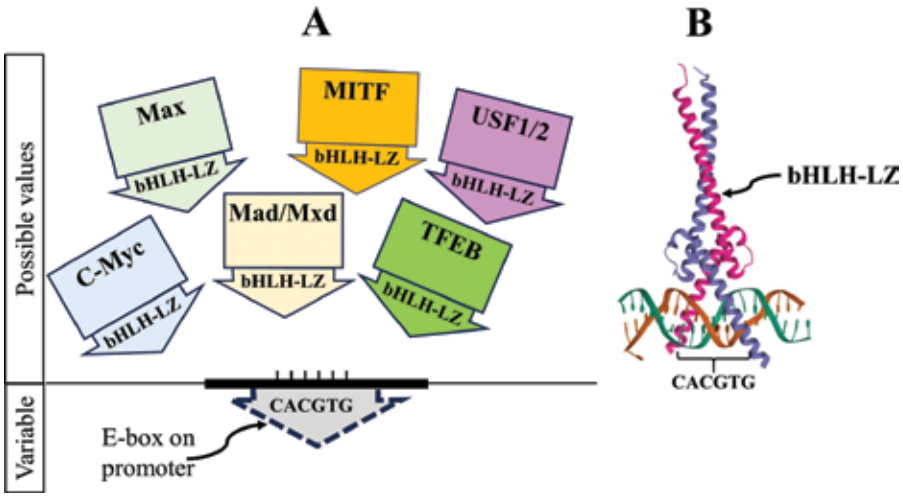

Figure 3. Six different transcription factors can bind to part of the human TERT promoter to regulate the telomerase reverse transcriptase gene (Khattar and Tergaonkar, 2017). A: The E-box (enhancer box) variable can be assigned any of 6 value types through binding to c-Myc, Max, Mad/Mxd complex, MITF, USF1/2, or TFEB using the distinctive bHLH-LZ protein domain. B: Chemical representation of the basic helix-loop-helix leucine zipper (bHLH-LZ) domain recognized by the sensing core part of the E-Box's consensus sequence 'CACGTG.' Source: Protein Data Bank, https://www.rcsb.org/structure/1nkp.

ecules. As an example, transcriptional activators and repressors can compete at the same binding locations, dynamically regulating gene expression by adjusting the relative proportions of the activators and repressors (Jacobs et al., 2023). Also, different combinations of enhancers (DNA sensors) can collaborate to produce a continuum response (Davidson, 2001; Jacobs et al., 2023).

Cellular Sensors Are Programming Variables

The above discussion was intended to clarify why cells should be viewed as information processors, more specifically, analog logic devices.

Variables are fundamental to communicating intention. In digital computers they are specific locations in the memory where values can be placed or extracted. Similarly, in biological cells, sensors are located at special locations to scan for signals (i.e., the values they are designed to recognize). We call these locations variables since logical operations will be performed there. In Part 2, several tables are provided with many examples of variables (sensors) physically located on DNA, RNA, and protein, along with the processes they regulate.

In human language and digital programming, rules specify how values are to be represented. For example, '10' is a valid integer, but '01' and 'X1' are not. In cells, however, values (i.e., the signals) must possess physical features to specify their validity for a sensor. An example is shown in Figure 3, which illustrates how only some TFs must bind to a class of DNA cis-elements, which act as sensors (Khattar and Tergaonkar, 2017). The rate of binding is stochastic and is defined by the concentration gradient of TF.

In digital computing, instructions are communicated explicitly as source and compiled code, whereas in analog computing, there are no instructions separate from the processing equipment. For cells to function autonomously, the variables and their values interact physically, which is true of all analog computing.

Variables Are Used to Express an Intended Outcome

We stated above that variables are fundamental to communication. Since our computational model of cells is intended to clarify the essential nature of thousands of processes, it seems worthwhile to review what variables are all about.

Once a variable has been assigned a value, decisions can be made. The sensor alone or a signal alone accomplishes nothing useful, as recognized by others (Farnsworth et al., 2013):

> "When two or more such configurations are brought into association, there is a combined arrangement, which if persistent, also instantiates information: that of both components plus that of their association."

For example, the Nuclear Localization Signal on proteins are sensors but alone does nothing until bound by importin-α and importin-β. Only jointly can RanGTP and other components be recruited, initiating a process that guides the protein through a Nuclear Pore Complex (Oka and Yoneda, 2018).

Indeed, many researchers use the vocabulary of information to interpret cellular processes, which will be reviewed in Part 3 of this series.

Although variables are implemented physically in analog computers and brains, they have properties that distinguish them from simple material interactions, as summarized in Table IV. The first property mentioned is specificity. To illustrate, cellular sensors must be clearly recognized by the kinase enzymes that are to phosphory-

Table IV. Characteristics of variables that distinguish them from unintentional physical interactions.

Property	Relevant to digital programming and human language	Cellular examples
They must be unambiguous.	Rules specify what variables are and distinguish them from each other.	Codons on mRNA must be recognized as different from the same triplets on random RNA.
They are abstract representations of objects or concepts.	'Best_option' 'Dog' 'Quantity'	Abundance_of_nutrient_x.
Operations can be performed with them.	Cost <= Price × Quantity	Accelerate or slow down the recruitment of proteins and assembly of complexes.
They are used to communicate an intention.	If Pressure > 500 Then Open_Valve.	If the receptor is bound to signal molecule X, then recruit protein Y.
Their purposes do not derive from their physical properties.	The physical structure of the string 'Set_price' is independent of its meaning and purpose(s) to be communicated.	The physical properties of a sensor specify what it will bind to, but are independent of the resulting process to be accomplished.
They can iteratively represent collections of other variables.	Animal = [Cat, Bear, Dog, Horse, Cattle] Dog = [Bulldog, Beagle, Poodle, Collie] Bulldog = {Rocky | Buster | George}	Binding site = [DNA, RNA, protein, sugar, etc.] DNA = [Enhancer, Promoter, Silencer, ori, etc.] Enhancer = [MyoD, Sox2, NF-κB, p53, AP-1, etc.]

late at that position. This explains why humans have >500 kinds of specialized kinases used in signaling networks. The number of targets for each kinase ranges from very few to hundreds, but importantly, each protein kinase must *avoid thousands of off-target phosphorylation sites* (Laub, 2016; Miller and Turk, 2018).

The last entry in Table IV notes that variables can be assigned other variables as their values. This helps to understand cellular processing by recognizing recurring generic patterns. For instance, the notion of a *binding site* applies to thousands of cases. In DNA alone, there are many kinds, such as enhancers and silencers. In addition, there are many variants of enhancers, depending on what they are designed to interact with.

Digital vs. Analog Programming

In modern digital computer programming, software is abstracted from the hardware. Programmers develop source code without considering its physical implementation, trusting that the instructions they program will be carried out.

This has led some to question whether cells are truly computers, since they do not recognize the kind of software coding they are familiar with. Furthermore, in cells, the physical processes can usually be described. For instance, an aminoacyl-tRNA synthetase can link an activated amino acid to a specific nucleotide at the 3′ end of the correct tRNA. As another example, the exact interactions of a codon with its cognate anti-codon can be described physically. These observations have led some to believe that cellular processes are merely chemical processes.

However, in principle, a materialist could "explain" all outcomes of computer programs by laboriously observing the physical processes occurring in the hardware, such as the flow of electrical signals through conductive pathways, the switching of transistors, and the alteration of charges in capacitors, which collectively execute the program's instructions. Clearly, such an approach would neglect the decisions made by humans that change the starting parameters, and, therefore, predictions cannot be made in advance about what a parametrized program will do.

Clearly, the fact that physical processes are involved does not demonstrate that cells are not information processors. In cellular analog programs, sensors serve as the initiating and regulating end of processes that assemble complex hardware to produce biologically important outcomes. This is clarified in Part 2 of this series, using the concept of immediate and major goals of cellular variables. To illustrate, the attachment of a hormone to the correct membrane receptor (the immediate goal) is only the initial step. It triggers a signaling cascade that ultimately regulates protein synthesis—either increasing or decreasing the production of specific proteins that

change specific cellular function (the major goal).

In cells, hardware and software are integrated for each process, creating individual *programs*. In contrast, digital variables and values are defined by combining symbols from a binary alphabet {0, 1}, using conversion rules. Thus, the decimal value '20' is represented in the ASCII code by the binary digit '10100.' Analog variables and values are also defined in cells by combining members of an alphabet of amino acids, nucleotides, lipids, sugars, and so on, but only portions of these molecules are directly (i.e., physically) involved in defining the distinguishing property of the variable.

Digital computational models discretize data, whereas analog computing leverages the natural properties of materials or systems, such as electrical voltage, fluid pressure, mechanical motion, or electromagnetic wave amplitude, phase, frequency, or polarization to perform their computations automatically (Gregersen, 2025). A feature of many modern analog computers is the patch panel, which allows users to physically connect different components to specify the configuration needed for a particular problem. The physical wiring defines the "program" that the analog computer will execute (Ulmann, 2022; Balci, 2023). Analogous to cells, once the "wiring" is set up, no source code is necessary.

Key details distinguish analog from digital computing processors (Roquet and Lu, 2014; Sarpeshkar, 2014; Munsky and Neuert, 2015; Grozinger et al., 2019; Waqas et al., 2020):

1. *Physical properties specify the outcome*. Analog decision-making relies on continuous *inherent* physical properties.
2. *Continuous outcomes are achieved*. Regulation of the rate of outcomes can be guided through continuous changes in the input.
3. *Direct response*. The magnitude of effect results automatically and is rarely linear.
4. *Signal integration specifies the outcome*. Multiple causal factors can be collectively integrated. For example, concentration gradients in cells can be modified by multiple factors that lead to an instant collective concentration. Therefore, the concentration of biochemicals has been called a *carrying signal* (Mogas-Díez et al., 2021). Also, cellular programs must often produce multiple effects that require tradeoffs (for example, the level of expression of multiple genes). The tradeoff logic can be rapidly calculated to adjust the informative signal (for example, concentration of TFs).

The analog nature of cellular processes explains why their continuous variables are often modelled using differential equations. In fact, historically, analog computers were designed to solve ordinary differential equations, revealing the conceptual link.

Given the physical nature of cellular sensors or variables, environmental factors like temperature, salinity, and pH can modify their responsiveness to binding partners. Therefore, these factors can also be deliberately adjusted in cells, leading to a far richer notion of variables than available to discrete variables. To exemplify, in a programming language like python

```
set_new_price = 100                (1)
```

expresses an invariant value unless the quantity 100 is changed. In the analog variable concept, a variable like set_new_price itself could assume different nuances, such that even the same value '100' would produce a different effect. Specifically, the responsiveness of sensors can be adjusted.

The notion of cellular variable inexactness might superficially remind one of *Fuzzy logic* (introduced by Zadesh, http://zadeh.cs.berkeley.edu/) used in discrete programming, but as elaborated on in Appendix 3, this is a different concept.

Variable inexactness or fine-tuning might also remind one of the concept of pattern matching used in digital programming, such as:

```
if current_ codon like 'CU%'    (2)

and is_bound_to_a_suitable_
anticodon

then

next_amino_acid = 'Leu'
```

This expresses that codons CUU, CUA, CUC, and CUG that satisfy the pattern 'CU%' should all be recognized as synonymous. In pattern matching, the alternatives that are satisfied act as synonymous, whereas the distinct structure of a cellular sensor interacting with a signal produces differences that affect the resulting outcomes.

Further Evidence of the Analog Nature of Cellular Programming

Further evidence of the analog nature of biochemical processing has been provided by the facile design of synthetic gene circuits able to detect specific cell states and perform state-specific control of desired protein expression (Prochazka et al., 2022). Especially relevant is the success of cytomorphic circuits technology, discussed in Appendix 4.

Cell membranes can be viewed as an interface for multiple external inputs using specialized receptors (Wurtz, 2021). The signals are encoded into an intracellular language that produces a signaling network able to summarize and coordinate all the incoming signals. The analog nature of signaling networks is emphasized by

the cell's ability to enhance the signal strength by enzymatically activating second messengers. The way intracellular signaling networks organize multiple inputs to regulate genes has been referred to as the biological equivalent of a computer's motherboard (Wurtz, 2021).

Research at the University of Edinburgh has revealed that living cells are physically wired in a manner analogous to computer chips, utilizing direct signals to instruct cellular functions (Duan et al., 2019). These insights have inspired the creation of synthetic biological computing devices using DNA, RNA, and proteins, using the same biochemicals and binding interactions found in cells (Benenson, 2012). Shared features include the use of sensors to interact with the exterior, hardware to process logic operations, and actuators to implement the logic output.

So far, we have shown that cellular sensors respond to stimuli in a continuous analog fashion. In Part 2, this will also be shown to apply to the subsequent assembly of the machinery to implement the intended processes. This is true because the biochemicals assembled produce their own new kinds of sensors.

A continuous range of each kind of outcome for cells is also achieved by using multiple receptor copies that are activated over a range of time periods.

Further Computational Insights from Cells

Cells have inspired some new computational models. The observation of template-guided splicing and recombination of DNA sequences (including deletions) to generate new or modified computational instructions inspired genetic algorithms (Daley and McQuillan, 2005; Finck and Beyer, 2009). A variant approach includes the use of pointers to combine fragments of programming code, inspired by how ciliates create their somatic genomes by rearranging genes in their compact germline genome (Rogojin, 2010; Nowacki et al., 2011).

Another concept is based on the use of physical compartments within cells to enable efficient processing. Within cells, there are membrane-enclosed compartments (organelles) that concentrate and constrain the proteins and RNA used in those locations. There are also dedicated regions that are not enclosed in membranes, such as cristae on mitochondria, Cajal bodies, PML Nuclear Bodies, Nuclear Speckles, Transcription Factories, Replication Factories, Chromosome Territories, Plasma Membrane Lipid Rafts, Synaptic Vesicles, Stress Granules, P-bodies, Adherens Junctions, Tight Junctions, Gap Junctions, and Nuclear Pore Complexes. This inspired membrane computing, also called P systems (Păun, 2000; Păun et al., 2009).

Summary and Conclusions

Cells display many features not found in human computing devices. They are technologies that manufacture their own hardware; adapt to changes in the environment; self-repair; recycle parts; and most significantly, reproduce themselves. Especially significant is a cell's ability to make adjustments along a continuum of values. This can be explained by their use of thousands of special sensors that can respond to continuous signals, especially concentration gradients. The sensing part of sensors acts as variables to which continuous values can be assigned. These values regulate cascades of processes that produce the changes required by cells.

Remarkably, cells can also manufacture the sensors themselves, modifying the copy number according to cell requirements. Interpreting cells as computing devices instead of a collection of chemical reactions provides a more productive interpretative framework. Researchers can begin their analysis by focusing on the logic being executed instead of the overwhelming amount of chemical detail.

The emphasis of Part 2 will be on the series of processes that are initiated by and regulated through the binding of signals to their receptors.

The intention of this 3-part series is to provide a new way to interpret what cells are. This is also a necessary foundation for our current research on how metaprogramming occurs in cells (Gudzyk, 2024). In computer science, metaprogramming is an established concept in digital programming whereby compact software instructions generate a broader executable code. Clearly, this occurs in cells. For example, a single gene can produce many copies of different protein variants (after mRNA splicing). The realization that analog sensors and programs are generated by cells will be addressed in the future. It offers a new paradigm in computer science, namely, that of metaprogramming being applied to analog computing.

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Appendix 1. Regulated cellular biochemistry does not resemble abiotic chemical behavior

Precisely regulated cellular biochemical processes are fundamentally different from familiar chemical processes, including designed laboratory oscillators, in many ways.

- *Specificity*: Changes caused by biochemical concentration gradients are site-specific (e.g., enzyme-substrate binding), unlike the generalized, non-specific reaction kinetics in non-cellular chemical systems.
- *Complexity and regulation*: Cellular oscillations involve intricate networks of genes, proteins, and feedback loops (e.g., transcription, translation, post-translational modifications), whereas chemical oscillators rely on very few simple molecules.
- *Precision and robustness*: Cellular systems maintain precise and robust control over concentration changes through mechanisms like redundancy and adaptive feedback. Simple oscillatory reactions are very sensitive to initial conditions and external perturbations.
- *Autonomy*: Once improper stoichiometric ratios develop over time, chemical oscillations terminate. In cells, the initiation and termination of such biochemical processes are regulated to satisfy whole-cell needs.
- *Adaptability*: Cellular systems adjust oscillation patterns in response to environmental cues or signaling, while chemical oscillators follow fixed, deterministic dynamics based on static chemical trajectories.
- *Stochasticity*: Cellular processes incorporate noise and stochastic events (e.g., gene expression variability), while chemical oscillators are deterministic and lack such randomness.
- *Single-purpose reaction pathways*: Chemical oscillators follow fixed reaction pathways without the multifunctionality of cellular systems.
- *Timescale*: Cellular oscillations (e.g., circadian rhythms, cell cycle) occur over minutes to days, regulated by molecular clocks, whereas chemical oscillators operate on much shorter, less flexible timescales (seconds to minutes).
- *Energy dependence*: Cellular oscillations are ATP-driven and tightly coupled to metabolism, whereas chemical oscillators are fueled by spontaneous redox reactions without biological energy currencies.
- *Purposeful output*: Cellular oscillations serve functional roles (e.g., homeostasis, division), whereas chemical oscillators are emergent phenomena without biological intent.
- *Multiple oscillating systems*: In cells, hundreds or thousands of processes occur in the same region for independent purposes, often with cross-talk between them.
- *Integration of multiple functions*: In cells, oscillations are often integrated with other processes (such as cell cycle progression or circadian rhythms) to coordinate broader cellular functions.
- *Replication in toto*: In cells, a multitude of biochemical processes are passed on in a functioning state to the daughter cell.

None of the chemical oscillations developed, conceived, or proposed by OoL chemists as precursors for ancient cells resembles the biochemical components or processes used in cells. Cellular biochemical processes must provide the metabolic and energy needs of the integrated and autonomous system as a whole. These rely on sensors to interact and adapt to the environment; enable mobility; interact with other cells; and reproduce.

Appendix 2. Codons must distinguish between identical but incorrect triplets

One way to distinguish cellular variables (i.e., sensors) from purposeless, random interactions is to examine the microenvironment where they interact with the target signals, as illustrated in Figure 4. One might incorrectly suspect that identical triplets located anywhere on mRNA and other RNA molecules could base pair at many locations on any tRNA. Instead, translation occurs rapidly and reliably, one triplet codon after the other. False interactions are avoided with the help of the surrounding regions. This illustrates how cellular sensors must be specially engineered to avoid meaningless interactions.

Reliable codon-anticodon interactions require precise engineering involving scores of enzymes (Sharp et al., 1985; Hopper et al., 2010; Hopper, 2013; Raina and Ibba, 2014; Hopper and Nostramo, 2019; Yu et al., 2019; Truman, 2020b, 2021). This is an example of how the signaling molecule and sensor must also be tailored. Human tRNAs contain, on average, 13 chemically modified nucleotides to ensure proper shapes and to prevent incorrect folds. The anticodon region of each tRNA is shaped into a niche that optimizes H-bonding with the codon triplets, despite each codon nucleotide having the cognate hydrogens in different locations (Yarian et al., 2002; Deutsch et al., 2012; Wang and He, 2014; Barciszewska et al., 2016; Pan,

2018; Roy et al., 2018; Huber et al., 2019; Krutyhołowa et al., 2019; Nguyen et al., 2020). Other modifications enhance proximate interactions with the ribosome to anchor the tRNA in place and prevent reading frame slippage (Hoffer et al., 2020).

Appendix 3. Fuzzy logic programming in digital technologies

In digital programming, techniques exist to process values in a more nuanced fashion than simple true/false decisions. For example, a variable 'Sick' could be assigned a Boolean value true or false. However, there are degrees of sickness, and this might need to be taken into account. In fuzzy logic, categories such as *very_sick*, *moderately_sick*, or *slightly_sick* could be defined to represent degrees or probability of sickness, each covering ranges of values based on some criteria. Programming logic would then be expressed for each of the possible categories.

In practice, continuous (analog) values are often divided into narrow discrete ranges so that digital programs can process them.

Appendix 4. Cytomorphic circuits

Cellular biochemical reactions have energy barriers that follow Boltzmann exponential laws that are also found in electronic flow when below the threshold voltage in transistors (Sarpeshkar, 2010, 2012, 2014; Daniel et al., 2013).

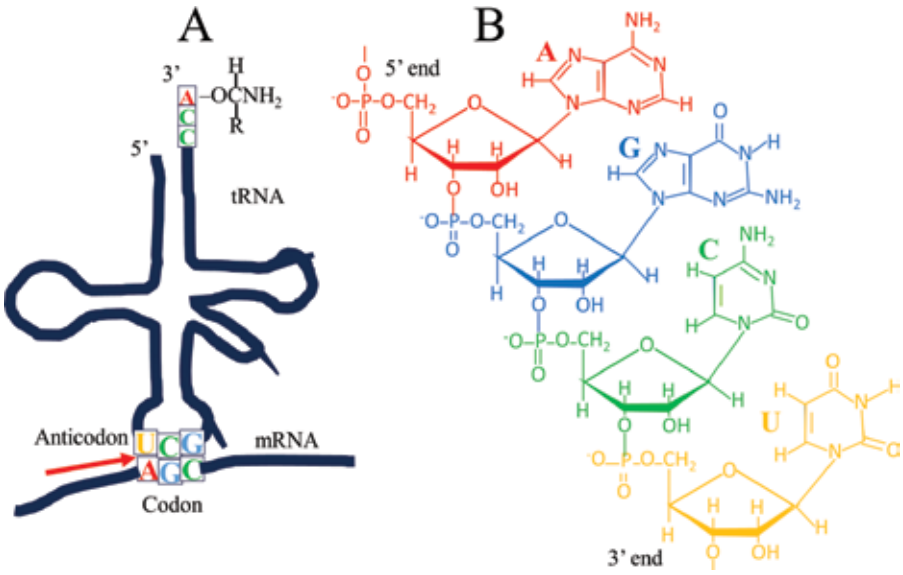

Figure 4. Codon triplets must not base-pair indiscriminately if they are to function as cellular variables. A: The red arrow points to the microenvironment where codons recognize the correct anticodons. B: Chemical structure of the nucleotides.

This mathematical similarity has led to the development of analog electronic "cytomorphic circuits" that are used to mimic cellular processes. Voltages represent molecular concentrations, and currents represent reaction rates (Daniel et al., 2013; Sarpeshkar, 2014; Hanna et al., 2020).

The core architecture of cytomorphic systems typically comprises specialized analog circuit modules called 'Protein Chips' (Beahm et al., 2021) that can model zeroth-, first-, and second-order reactions, including nonlinearities and interactions. By connecting multiple transistor circuits, researchers can faithfully reproduce cascades, loops, fan-in, fan-out, dimerization, and other biochemical network patterns (Beahm et al., 2021; Waqa et al., 2022). Unlike digital simulations that discretize continuous biological processes and solve them iteratively, analog cytomorphic circuits can instantly integrate all the inputs just like cells can (Coldewey, 2016; Woo et al., 2018; Beahm et al., 2021). Acceleration and conceptual simplification of the modelling effort are necessary since gene-protein networks involve tens of thousands of state variables that interact through elaborate feedback loops (Sarpeshkar, 2014; Beahm et al., 2021).

Analog Neuromorphic Circuits

Another technology used to mimic biological analog processing is neuromorphic circuits. These are a type of electronic circuitry using Complementary Metal-Oxide-Semiconductor (CMOS) circuits designed to imitate how brain neurons and synapses are thought to function (Indiveri et al., 2011; Hazan and Tsur, 2021; Chen et al., 2023; Xiao et al., 2024; Yoon et al., 2024). They perform analog parallel processing very effectively, closely mimicking brain neurons and consuming far less energy than conventional computers.