Cells Are Integrated Multiprocessing Analog Computing Devices—Part 2

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Abstract

Cells comprise thousands of intricately designed analog computing units that execute complex biochemical processes. Precisely positioned sensors—implemented in DNA, RNA, proteins, lipids, and other biomolecules—respond to continuous signal gradients and generate localized microenvironments that recruit, assemble, and regulate molecular machinery essential for cellular function. These sensor–signal interactions initiate stepwise processes that distinguish an immediate physical recognition goal from a downstream major functional goal, enabling fine-tuned control of rates, timing, and outcomes. Cross-communication among concurrently operating processes supports coordinated adaptation, repair, recycling of obsolete components, and system-wide reproduction while maintaining uninterrupted operation. Cellular logic is implemented through physical interactions, adaptor molecules, and dynamically assembled complexes that realize flexible 'if–then' relationships. Unlike conventional digital computers, cells do not separate software from hardware; instead, both are inseparably embodied in adaptive molecular structures whose sensitivities can be modified during execution. This analog computing paradigm provides robustness, scalability, and efficiency that differ fundamentally from digital computation and from purely chemical descriptions. Viewing cells as integrated multiprocessing analog computing devices offers a unifying framework for understanding cellular regulation, autonomy, and biological information processing.

Simple Summary

Biological systems function as integrated analog computing devices rather than following the rigid binary logic of modern digital computers. Instead of separating software from hardware, cells utilize adaptive molecular structures where physical sensors directly interact with continuous environmental signals to regulate growth and repair. These interactions facilitate a stepwise logic processing method, utilizing adaptor molecules and dynamically assembled complexes to achieve complex functional goals. By viewing cellular regulation through this analog computing paradigm, researchers can better understand the robustness and scalability of biological information. This framework highlights how cellular sensors and signals can be physically modified during execution, allowing for a level of fine-tuning and flexibility unattainable by conventional technology. Ultimately, the sources propose that metaprogramming principles enable cells to autonomously self-regulate and reproduce through these sophisticated, non-digital mechanisms.

Introduction

Bacterial and eukaryotic cells are far more than a collection of complex chemical reactions contained in a membrane. Cells autonomously organize and regulate their own growth, adaptation, protection, repair, and recycling, reproducing generation after generation in a constantly functional state. These processes require cells to manufacture both their own chemical components and usable energy.

In Part 1 of this series, we proposed viewing cells as an integrated series of analog computing devices. Thousands of bacterial and eukaryotic sensors interact with concentration gradients and other continuous signals. These sensors function as programming variants that initiate and regulate the biochemical processes necessary to fulfil the necessary functions mentioned above. Focusing on the logic processing provides a unifying overview that allows many chemical details to be neglected to focus on the essential.

Cells Do Not Function Like Familiar Digital Computers

A point emphasized in Part 1 is that cells do not have software that is separate from the hardware, unlike modern digital computers.

Digital computing depends on infrastructure capable of existing in only two distinct states. These binary units, or bits, are combined to encode variables, values, and logical operations, governed by formal rules and structured programming languages. The two distinct states are defined by magnetic polarity, light pulses, range of voltage, and other physical methods. Engineering specifications define an error tolerance so that only distinct states are used.

Before the codon → amino acid mapping used by the genetic code was understood, scientists already assumed that protein sequences were stipulated through some kind of code (Hayes, 1998). Once the genetic code was elucidated, it became common practice to assign the single letters A, C, G, and T to DNA nucleotides and one or three-letter abbreviations to amino acids (e.g., A, C, D or Ala, Cys, Asp). This created a mental association with known technical codes like the Morse and ASCII codes and computer programming languages. Furthermore, Shannon's *information* theory was developed before the genetic code was deciphered, which deals with the transmission of strings of symbols. Consequently, *information* and sequences of letters became linked in the minds of molecular biologists. Decoding mRNA messages seemed to resemble computer programming:

If current_codon = x then amino_acid = y (1)

For example,

If codon = CUA then amino_acid = Leu
If codon = GUC then amino_acid = Val (2)

where Leu is the abbreviation for leucine, and Val for valine.

Although nobody doubts that DNA specifies protein sequences, doubts are expressed about whether DNA represents a computer-like program. Where is the source code? Is the genetic code the only true code found in cells (Lesne, 2023)? (Cellular codes are discussed in Part 3 of this series.) Where do the instructions come from to assemble entire body parts and organisms? Some even insist that cellular processes can be reduced strictly to physical and chemical principles (Sarkar, 2005; Rosenberg, 2006; Bickle, 2010) and that comparisons with computers are only an anthropomorphism or a weak analogy (Nicholson, 2019).

An understandable mistake has been to associate cell processing too strongly with familiar digital computing. In Part 1, we identified sensors as variables, emphasizing that the sensing element directly interacts with a continuous gradient signal. This permits the response to a signal to be adjusted through physical modifications to a small microenvironment. Clearly, this is not how digital variables function. An assignment statement like *new_price = 100* cannot be programmed to produce a different meaning than 100 by modifying characteristics of the composing symbols (e.g., *n*, *e*, *w*, *p*…) that compose the variable '*new_price*.' But as discussed in Part 1, this is how cellular programming is fine-tuned. Reflecting on synonymous codons helps to clarify this distinction. In some cases, only the first two nucleotides uniquely specify the amino acid, and the third 'wobble' position modifies the probability that the codon will be translated correctly. Many overlook that only a small portion of the nucleotides is responsible for anticodon identification, namely, specific H-bonds.

To illustrate, in *E. coli,* the codon *AGA* is usually translated to arginine, but *AGA* is sometimes mistranslated to the similar amino acid lysine due to the similarity at the binding location and the low concentration of the anticodon for AGA that translates to Arg, $tRNA^{Arg}$(UCU). Consequently, the AGA codon sometimes recognizes a $tRNA^{Lys}$(UUU) (Sun and Zhang, 2022). This is not a feature of digital programming, whereby variables and values in the same programming instruction have a unique meaning.

Analog Computing Technologies

Analog computing was discussed in Part 1. It uses technologies having a direct physical connection between changes in an input variable (such as a concentration gradient, temperature, pressure, and light flux) and an outcome. We believe that all or virtually

all cellular programs are implemented using analog computing principles. Some processes, like chromosome replication, are executed only during the lifespan of a cell, whereas others are replicated and passed in a running state to daughter cells (Handy et al., 2011). Some process details can be inherited by future generations by modifying DNA sequences or using epigenetic tags (Powledge, 2011; Fitz-James and Cavalli, 2022; Tollefsbol, 2022).

The analysis in Part 1 emphasized the key role of sensors, which act as analog variables. Sensor values correspond to the setting along the X-axis of the example shown in Figure 1. Physical adjustments to a sensor result in different response sensitivities, changing binding strengths or rates. But such physical-chemical effects are only the initiating and regulating part of the cellular processes executed. We introduce now the concept of an immediate physical goal to be met by analog variables vs. the implied major goal to be achieved.

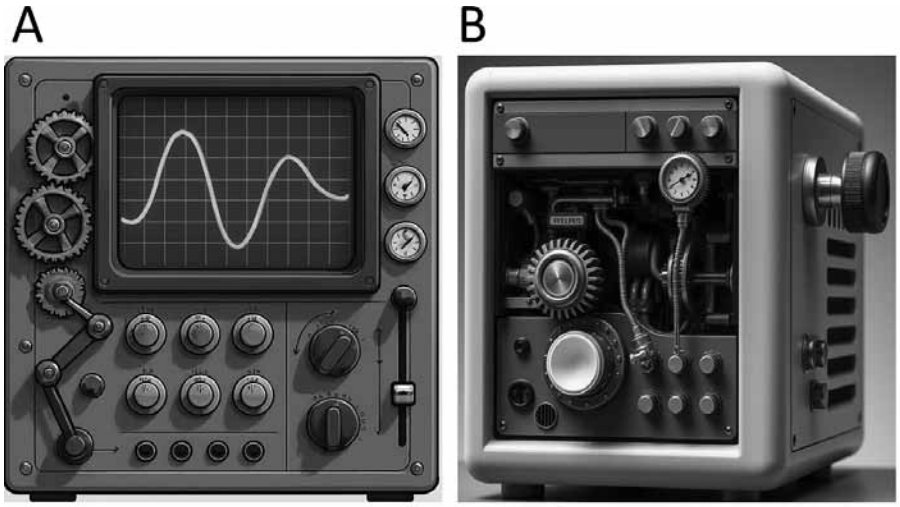

Figure 1. Fictitious analog computers illustrate how continuous physical or mechanical changes in an input variable produce continuous changes in the response. (Image generated by AI).

Immediate Goal of a Cellular Variable ('Step 1')

The immediate task of a sensor is to recognize changes in the signal. In Figure 1, the sensor must be engineered to immediately sense changes in lever position, or dial rotation, or whatever is used to define a continuous input value. For instance, the first goal a codon must satisfy is to identify the intended anticodon on a tRNA defined primarily by ~5 – 9 suitably positioned hydrogen bonds[1], plus stabilizing contributions from portions of neighboring nucleotides in both the tRNA anticodon stem loop and the mRNA (Gorochowski et al., 2015; Nedialkova and Leidel, 2015; Mala and Saraogi, 2022). Post-transcriptional modifications in the anticodon region also contribute to the accuracy and speed of this interaction (Mala and Saraogi, 2022). This physical dependency explains why the composition and abundance of the tRNA pool (which vary in cell- and tissue-dependent manners) are used to regulate mRNA translation velocity (Nedialkova and Leidel, 2015; Davyt et al., 2023).

The general principle is that the effectiveness of the association between cellular variables with values is determined by the geometrical and electrostatic characteristics at the micro-location where the identifying interaction occurs. These sensor locations are strategically located on DNA, RNA, protein, sugar, phospholipid bilayer, etc. For example, a portion of a receptor tyrosine kinases (RTKs) on the outer cell membrane must recognize the defining portion of an extracellular signaling molecule (Laub, 2016). Many studies have helped elucidate the physical basis of sensor interactions that specify the *immediate goal*, but it is important to realize that this is only a means to an end, namely, the conversion of an input informative signal into a downstream process, discussed next.

Major Goal of a Cellular Variable ('Step 2')

Once a sensor has bound to a gradient signal, the next cellular processes can be initiated and regulated. For example, only after the stable codon to anticodon interaction has been established will the next steps occur to carry out the translation.[2] Changes in total bind-

1 Pairing between nucleotides C and G uses 3 H-bonds and pairing between A and U uses 2 H-bonds. However, in the wobble position of tRNA, Inosine (I) arises from the deamination of A by the enzyme ADAR. A with I pairing uses only 1 H-bond (sometimes with a weak contribution from a second H-bond). Therefore, the codon AUA when paired with the IAU anticodon uses only 5 H-bonds. When three C with G interactions are involved then 9 H-bonds are used.

2 After codon-anticodon pairing, a peptide bond forms between the amino

ing strength and the concentration of tRNA regulate the rate at which these subsequent steps will be initiated, ensuring the correct concentration of protein will be formed. Individual codon translation rates also regulate the process so that sufficient time is available at key protein locations to permit proper folding (Fluman et al., 2014; Faure et al., 2017).

As another example, binding of a signal molecule to a sensor kinase ('Step 1') is followed by autophosphorylation of a histidine amino acid, transfer of the phosphate to another response regulator protein, and then several more steps to modify the expression of several genes (Laub, 2016). The latter constitute 'Step 2,' i.e., the major goal.

Cells possess a distinguishing characteristic that differentiates them from natural chemical processes and all human technologies to date. The processes initiated and controlled by sensors cause a pre-planned assembly of the requisite processing equipment (e.g., molecular machines). Astonishingly, these processes produce new microenvironments that become new sensors that bind to new partners. This permits cellular goals to be regulated along the whole execution chain.

Flexible Programming of Step 1 and Step 2

Programming requires intentions to be expressed using logical operations. Cellular 'reasoning' is implemented by adding, removing, and modifying details during process execution. A sensor provides the 'If' part of a program, namely, if the signal is sensed long enough to begin the processes to achieve the intended outcome. Recall that the sensitivity of the variable (sensor) can be modified in many ways (e.g., using ligand attachments, chemical modifications, cofactors, different pH and temperature, etc.), and influences from different kinds of sensors can be integrated to fine-tune control.

The sequence of activities along the chain leading towards the major goal also has the character of If…Then. When the sensor plus signal microenvironment recruits the first biochemical(s), a new sensor is generated (or was already incorporated into the recruited partner) at a precise location. This self-assembly cascade thereby produces a new, just-in-time cellular process. Throughout all these activities, Boolean AND, OR, and NOT logic can be implemented using physical interactions.

Implementing If…Then logic in cells often relies on the concept of adaptor molecules or adaptor complexes.

Adaptor Molecules and Complexes in Cellular Processing

Recognition of a signal by a sensor is used as the 'if' part of cellular decision-making, and the decision must be physically transmitted to have any merit.

Two examples are shown in Figure 2, involving the concept of adaptor molecules or adaptor assemblies. In Figure 2-A, one end of the tRNA adaptor molecules is recognized by a codon during Step 1. Since the other end of that tRNA has already been charged with the correct amino acid, the next step can be implemented. The reasoning is, for example,

> If a tRNA having anticodon 5′-UCG-3′ binds to an mRNA codon, then add amino acid serine to the growing polypeptide chain.

This flexible design strategy permits different correspondences between n codons and 1 amino acid to be implemented by using different sets of tRNAs.

Figure 2-B shows how a cascade of If…Then logic is often found in cells to assemble and execute the machinery stepwise that implements cellular processes. Initiating RNA transcription is an example. To initiate the process, the ~ 8-nucleotide (~8 nt) sequence TATA box sensor binds to part of a TATA-binding protein (TBP). Once TBP is bound to the TATA box, a series of proteins are recruited stepwise by generating a recognition region for the partner it should interact with. Eventually, the preinitiation complex (PIC) is formed. Part of this PIC then interacts with the RNA polymerase complex to position it correctly so that it can begin transcription. The TIP acts like an adaptor complex linking the TATA-box with its activating signal to the processes involved in transcription.

The diagram in Figure 2-B illustrates how, sometimes, it can be somewhat arbitrary which partner is assigned the role of sensor vs. signal. What matters is that the binding interaction is what specifies what is to result. Generally, if the concentration of one variable fluctuates rapidly and considerably, causing a continuous change in output, then that partner is best viewed as the signal. Ambiguity can still result, since cells also often regulate the number of sensors according to need to become more responsive to changes.

These examples answer the concern that to be codes or programs, a correspondence must be changeable (Lesne, 2023). We have just shown that in cells they are indeed. For instance, in the *N*-end *ubiquitin code,* the first position

acid in the A site and the polypeptide chain on the P-site tRNA, transferring the chain to the A-site tRNA. During translocation, the ribosome shifts one codon, moving the empty P-site tRNA to the E site and the A-site tRNA (now with the polypeptide) to the P site. This opens the A site for the next aminoacyl-tRNA.

of a protein communicates the half-life of a protein (Varshavsky, 1997), ranging from arginine $t_{½}$ ~2 minutes up to methionine $t_{½}$ >20 hours (Sriram et al., 2011). This code could have been designed in many ways, since the choice of what each residue should specify is arbitrary. Implementing any of the possible codes could then be engineered by ensuring correct interactions with the protein degradation enzymes.

However, as discussed later in Part 3, the ambiguous term *code* often leads to misunderstandings, since the term has several meanings in the literature.

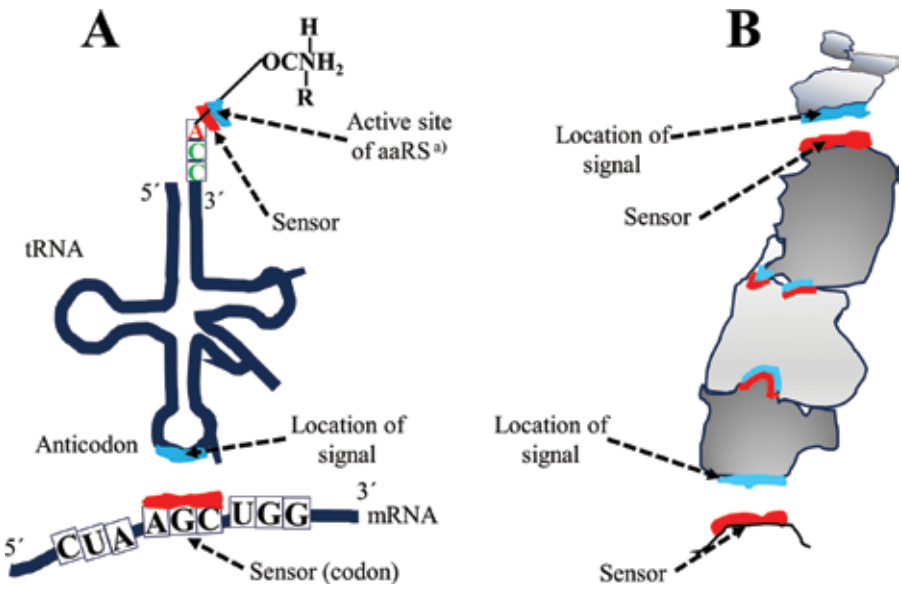

Figure 2. Adaptor molecules are a key strategy used in cells to implement processes flexibly. A: A single adaptor molecule connects a specific sensor to a specific process. The example shows a tRNA. (Other portions of the t-RNA adaptor molecule also interact with parts of the ribosome to ensure correct processing.) B: An alternative design more frequently used in cells links multiple components (proteins and / or RNAs) with each component possessing both a sensor to identify its partner and a recognition portion elsewhere for the sensor of a different component. This stipulates how the machinery is to be assembled and processed stepwise. Red lines indicate sensors and blue lines the recognition signals. a) aaRS = aminoacyl-tRNA synthetases

Sensors Defined Using DNA

Cellular sensors can be engineered using DNA, RNA, proteins, carbohydrates, or lipids as the medium. Some examples of variables located on DNA that are used to regulate important cellular processes are provided in Table I. Only enough examples were provided to exemplify the principle.

The first column documents the cellular process being referred to. The second column mentions what the sensor is, namely, the analog variable used to initiate and regulate the entire process. In column 3, the distinctive sensing feature within the sensor is identified to distinguish it from the surrounding housing (i.e., the casing or enclosure). The housing ensures proper functioning of the sensing feature and helps distinguish it from false sensors. For example, anticodons must not bind to random nucleotide triplets. The fourth column identifies the informational signal the sensor was designed to recognize. It is restricted to only the relevant distinguishing feature, since very often they are also enclosed in an optimizing housing. For example, on average, a protein like a transcription factor (TF) could bind at >3,500 locations with a relevant-size DNA counterpart (Tompa and Rose, 2011). False interactions must be avoided by ensuring a precise fit between the binding partners.

In the fifth column, refining components and activities are documented that serve a quality control function, ensuring the sensor is interacting with a legitimate signal. Often, cofactors, ligands, and other biomolecules are also involved to strengthen the binding interaction. Column six documents some of the biochemicals and complexes that are assembled at the microenvironment where the sensor is interacting with its signal. These execute the useful cellular functions intended by the sensor.

How far a researcher wishes to document the intended outcome depends on what is being studied. For example, the major goal ('Step 2') for eukaryotes could be identified as the generation of primary RNAs if one wishes. Others may continue to describe how RNAs are then used to code for proteins or regulatory functions, and so on, even until specific biological outcomes are achieved. Our model is recursive. Sensors are created dynamically and used by cells in linked chains of processes.

The last column is not intended to be an exhaustive list of the references we used to reach our conclusions.

The processes mentioned in Table I will not be discussed in detail to avoid excessive side-tracking details.

A nuance of DNA-based sensors involves regulating DNA expression and replication by binding to an RNA copy.

Table I. Examples of cellular variables located on DNA and the bio-components involved.

Cellular process	Sensor	Sensing feature	Signal recognized by the sensor	Quality control (QC) and stabilization (Stab) of the sensor with signal	Complexes recruited during subsequent processes	References
Initiation of DNA replication in *E. coli*	DnaA boxes within the origin of replication site (ori)	Consensus 5′-TT(T/A) TNCACA-3′ pattern	Helix-turn-helix domain of DnaA	QC: A threshold of multiple DnaA molecules must bind cooperatively. Also, catalytic hydrolysis of ATP on DnaA leads to an ADP-bound form that prevents reuse of the ori. Stab: IHF, Fis, and DiaA.	DnaC binds; DnaB helicase is loaded onto single-stranded DNA; DnaC is released; DnaG associates with DnaB, forms the primosome.	Wegrzyn and Konieczny, 2024
Elongation of DNA in *E. coli*	Individual nucleotide positions on the template strand	Individual A, C, G, and T nucleotides.	Complementary dNTPs positioned in the alpha subunit of Pol III.	QC: Pol III performs proofreading via an induced-fit and 3′–5′ exonuclease activity. Stab: Using a Pol III structuring pocket and Mg^{2+} to coordinate the phosphate groups.	After phosphodiester bond formation, the sliding clamp ensures processive movement of Pol III along the template.	Łazowski and Woodgate, 2024
Initiation of transcription in eukaryotes	TATA box within the promoter region	6-8 nt pattern resembling TATAAA	Part of the TATA-binding protein (TBP)	QC: General transcription factors, including TFIIA and TFIIB. Stab: Activator proteins bound to enhancers	Additional TFs to form the preinitiation complex that positions RNA polymerase II.	Haberle and Stark, 2018
Transcription in eukaryotes	Nucleotide position on the template DNA	Individual nucleotides (A, C, G, and T)	Complementary rNTP in the active site of the RPB1 subunit of Pol II	QC: Pol II with TFIIS execute proofreading. Stab: Using TFIIB, TFIID, Mediator complex, ATP-dependent chromatin remodeling complexes, histone modifications, and various coactivators.	Several elongation factors associated with Pol II to ensure its processive movement.	Svetlov and Nudler, 2013; Su and Vos, 2024
Base excision repair (BER) in most organisms	Damaged nucleobase on a nucleotide	Nucleobase shape after oxidation, alkylation, deamination, etc.	Structurally complementary active site of DNA glycosylases	QC: Glycosylases flip the nucleotide into their active site pocket to check shape complementarity. Stab: Mg^{2+}, XRCC1 and APE1, phosphorylation and acetylation of glycosylases, histone modifications, and chromatin remodeling factors.	Repair complex including an AP endonuclease, DNA polymerase, and DNA ligase.	Chen et al., 2024
Global genome nucleotide excision repair in humans	Location of bulky DNA lesions that distort the DNA helix	Cyclobutane pyrimidine dimers, chemical attachments, etc.	A beta-hairpin motif in a DNA-binding domain of the XPC protein	QC: XPA acts as a damage verification factor; also, the XPB and XPD helicases. Stab: Using RAD23B, Centrin-2, TFIIH complex, and RPA. Also, ubiquitination and sumoylation modifications of XPC.	XPG and XPF-ERCC1 endonucleases, DNA polymerase, and DNA ligase.	Scharer, 2013; Chen et al., 2024
Mismatch excision repair (MMR) in humans	Locations of DNA base mispairing	Wrong base-paired shape after insertions and deletions	Complementary domains in MSH6 subunit of MutSα, and MSH3 of MutSβ	QC: MutLα complex to verify the mispairing. Stab: PCNA and RFC; and also RPA.	Exonuclease 1 (EXO1), DNA polymerase δ or ε, and DNA ligase.	Chen et al., 2024
Remove IES in Paramecium micronucleus	Regions at boundaries of MDSs and IESs	Short pointer sequences	Part of the PiggyMac (Pgm) protein	Both quality-control and stabilization rely on small RNAs and their Argonaute partners as well as chromatin markers.	PgmL, Ku70/Ku80 heterodimers, IV and XRCC4 proteins, nucleases, DNA processing enzymes, and NHEJ.	Rogojin, 2010; Bétermier et al., 2023

We view the sensor as being located on the DNA, with the copy number of RNAs serving as a concentration gradient (signal). Some examples include:

- R-loops form in a controlled manner to regulate transcription, DNA replication, and repair. They typically recruit protein factors that mediate downstream effects.
- Promoter-associated RNAs work in many cases together with protein complexes to fine-tune transcription initiation.
- Long non-coding RNA Xist, which is expressed from and coats one X chromosome in female mammals. Xist recruits protein complexes to ensure transcriptional silencing.

In some cases, binding interaction between RNA and DNA is designed to deactivate processes that would otherwise occur and don't require proteins:

- Triplex structures form Hoogsteen or reverse Hoogsteen base pairing that affect transcription by physically blocking TFs or RNA polymerase from binding.
- G-quadruplex structures form at G-rich DNA regions to influence gene expression by restricting DNA accessibility.

Sensors Defined Using RNA

Thousands of RNA locations need to be precisely targeted for chemical modification, especially on rRNA and tRNA molecules (Liu et al, 2025). Sensors are located at these regions that identify complementary patterns called guide sequences ~10–20 nt (nucleotides) that are found within snoRNAs ~60–300 nt long. In Box C/D snoRNAs, the guide sequences are usually located near the 5′ end, whereas in Box H/ACA snoRNAs, the guide sequences are generally located near the 3′ end. Once bound to the target RNA, another region of the snoRNA recruits enzymes that modify a specific nucleotide, performing 2′-O-methylation or pseudouridylation. There are about 1,740 sno genes (SKI-related proto-oncogenes involved in regulating gene expression, cell growth, and signaling pathways) in the human genome, grouped into 226 families (Zhang et al., 2016).

As a second example, mRNAs must often be downregulated and contain a sensor ~6–8 nt long located in their 3′ untranslated region (3′ UTR). These variables recognize complementary 'seed regions' usually located at the 5′ end of the miRNA that are RNA molecules ~22 nt long. Once the sensor and signal are bound, other complexes are assembled, typically leading to translational repression or mRNA degradation. There are approximately 2,300 human miRNAs (Alles et al., 2019) and many thousands of mRNA targets (Chen, 2025).

Some examples of variables implemented on RNA are provided in Table II, analogous to Table I. Reminiscent of codon to anticodon binding discussed above, it is the concentration gradient of the signal that specifies the rate and degree of the resulting outcome in these examples.

Nucleotide Pairing as a Principle Used by Some Sensors

Given the precision of nucleotide A-T and C-G pairing, nucleotide sequences are an effective design strategy for sensors to identify various concentration gradients. The specificity of the interaction ensures that the *immediate goal* of the cellular variable is fulfilled unambiguously more efficiently and compactly than usually possible from hybrid protein-nucleotide interactions.[3] Illustrative examples include:

- Identification of anticodons of tRNAs by codons (Kim et al., 2024).
- Identification of the correct region of U1 snRNA by the GU pattern at the start position of an intron during mRNA splicing. The branch site nucleotide recognizes the correct nucleotide of the U2 snRNA. But remarkably, the end position of the intron, defined by an AG pattern, identifies a region of the U2AF *protein* instead of an RNA molecule (Karijolich and Yu, 2010; Tholen, 2024).[4]
- The *miRNA recognition element* on an mRNA recognizes the seed region of the correct miRNA that is to regulate it (O'Brien et al., 2018; Prochazka et al., 2022; Bofill-De Ros and Ørom, 2024; Diener et al., 2024).

Reversal of the Role of Sensor and Signal

Generally, we consider the sensor to be the more stationary member of the physical interaction, and the copy number of the signal is what changes. However, the number of cellular sensors is usually also regulated. For example, the copy number of mRNAs and complementary tRNAs is both regulated. Alternatively, the number of TF copies is carefully regulated, whereas the target DNA-binding sites remain fixed in a cell (although some could be silenced).

To which binding partner the sensor and signal are assigned does not affect the analog nature of cellular computing, since it is the *change in concentration of bound states* that specifies the rates of the resulting processes.

Sometimes sensors appear to be rather passive and respond to signals if and when they arrive. In other cases, the sensors seem to play a more active

3 The use of RNA molecules in cellular processes, especially ribosomes, has been used as evidence for the RNA World hypothesis (Michael and Joyce, 2012). This overlooks that using RNA as an adaptor molecule makes sense as a design strategy.

Table II. Examples of cellular variables located on RNA and the bio-components involved.

Cellular process	Sensor	Sensing feature	Signal recognized by sensor	Quality control (QC) and stabilization (Stab) of sensor with signal	Complexes recruited during subsequent processes	References
Remove introns from pre-mRNA	5′ splice site 3′ splice site Branch point	GURAG consensus AG and polypyrimidine tract yUnAy (y = pyrimidine, A = adenosine, n = any nucleotide)	U1 snRNP U2AF heterodimer SF1	QC: G +1 position of intron; Suppression of Splicing (SOS) Stab: Other complementary nucleotides. QC: Distance to Branch Point Stab: Splicing factor FUBP1 QC: Competition between SF1 and QKI Stab: U2 snRNP.	Scores of proteins and RNA which form the E, A, B, B^{act}, B*, C, C*, P and ILS complexes.	Shi, 2017
mRNA regulation by miRNA	miRNA recognition element on mRNA	miRNA seed complementary sequence	6 to 8 nucleotide Seed Region of miRNA and Argonaute protein	QC: kinetic proofreading steps. Selective sorting of specific miRNAs into different AGO proteins Stab: GO protein.	RNA-induced silencing complex (RISC).	Jameel, 2023
Translation of mRNA	Position of codon on mRNA	Codon sequence	tRNA anticodon	QC: Multi-step kinetic ribosomal proofreading. Stab: Proteins and rRNA at the A site.	Proteins and rRNA involved in the elongation cycle and termination processes	Ramakrishnan, 2002; Schmeing and Ramakrishnan, 2009
Chemical editing of tRNAs. ~27 kinds in humans	Location where editing should occur	Specific nucleotide and surrounding structure on the tRNA	tRNA-recognizing active site of editing enzymes	QC: 3D recognition elements on the tRNA are recognized by the enzyme. Stab: Auxiliary protein factors and cofactors.	27 different enzymes / complexes.	Kirchner and Ignatova, 2015; Lorenz et al., 2017; Agris et al., 2018; Modomics, 2025
Chemical editing of mRNA. ~11 kinds in humans	Locations where editing should occur	Specific nucleotide and surrounding structure on the mRNA	mRNA-recognizing active site of enzymes	QC: 3D recognition elements on the mRNA are recognized by the enzyme. Stab: Auxiliary protein and cofactors.	Proteins involved in transcription, localization, translation, degradation, cell death, differentiation, etc.	Eisenberg and Levanon, 2018; Wilkinson et al., 2022; Modomics, 2025

role, searching for their partners. In the latter case, sensor concentrations are regulated and scan their environment (for example, in immune system responses to protect the cell). In both scenarios, the design principles remain the same. Distinctive sensing features are located in sensors; precise signals are recognized that avoid false bindings; quality control measures are used; and stabilizing co-factors are involved. Most importantly, initial recognition and binding are followed by the recruitment and assembly of the machinery needed to perform the intended processes (e.g., destroy all the invading viral DNA). Some examples include:

- Bacteria and archaea store snippets of viral DNA in their CRISPR loci. These become part of a sensor placed on small guide RNAs (gRNAs). These gRNAs target and associate with Cas9 protein (or a similar Cas enzyme) to form a ribonucleoprotein complex. The complex surveys 4–8 bp (base pairs), typically palindromic unmethylated sequences of invading viral DNA, and binds when a

complementary sequence is found. Cas9 then cuts the viral DNA at the targeted site (Loenen et al., 2014).
- Small interfering RNAs (siRNAs) primarily target mRNA for degradation or inhibit translation. But in some cases, siRNAs are used as sensors that guide methylation enzymes to DNA to suppress all transposons (Mahfouz, 2010; Xie and Yu, 2015).
- In animal germline cells, piRNAs target complementary transposon sequences (Ozata et al., 2019). This binding then recruits Piwi proteins and assembles the Post-transcriptional Gene Silencing (PTGS) complex. Potentially dangerous transposons are silenced through mechanisms including histone modifications, DNA methylation, and post-transcriptional degradation of transposon transcripts.

A distinguishing feature seems to be that the sensor gradient is now always regulated to be high enough to eliminate *all* the damaging effects, instead of the cell having to produce a *fluctuating* optimal amount of 'Step 2' processes.

Sensors Defined Using Protein Sequences

Portions of proteins are also used as sensors, as illustrated in Table III.

These are only a handful of the thousands of examples present in cells. For example, there are far more kinds of receptors on the cell surface than shown in Table III. Humans have >800 different kinds of G-protein coupled receptors (GPCRs; Casadó and Casadó-Anguera, 2023) that are involved in metabolic regulation and many other physiological processes (Vidad et al., 2021). Humans also have about 58 kinds of receptor tyrosine kinases (RTK) (Cattaneo et al., 2014; Kumar and Hassan, 2023, pp. 245–276), 30–40 cytokine receptors (Brooks, 2017, pp. 1–29), and many other kinds of receptors. Tragically, improperly regulated intracellular signaling pathways often lead to cancer (Du and Lovly, 2018).

Programming Advantages of Using Analog Processes in Cells

Regulating cellular processes by variables able to respond to continuous gradients offers several advantages.

1) *Fine-tuning of effects*. It is advantageous to respond optimally to changing requirements. Changes can be ramped up or down as needed, avoiding waste. For example, the grade of DNA methylation in a gene's promoter—defined as the mean fraction of methylated CpG—defines distinct levels of gene expression and is inversely correlated with gene expression level (Palacios et al., 2024). DNA methylation patterns can also be inherited, creating a form of analog memory.

Quantitative transcriptional regulation can also arise in an analog fashion through multiple histone modifications around the local chromatin environment of a gene (Antoniou-Kourounioti et al., 2023).

Eukaryotic genes can have hundreds of enhancers to which TFs can attach. This provides a strategy to rapidly incorporate a variety of signals to compute an optimal decision. As another example, in the splicing code, multiple enhancers and silencers can be used to specify the probability of incorporating or skipping various exons into the mRNA, producing different ratios of alternative protein variants (Wang et al., 2006; Barash et al., 2010).

2) *Simplification of logic programming*. In principle, a digital form of programming could be used to interpret concentration gradients by dividing into discrete ranges and using digital-style logic for each interval. Since the necessary outcome need not be a linear function of the gradient, this would be a very complex and resource-intensive design. Instead, the molecular machinery attached to cellular sensors is engineered to physically automatically respond appropriately.

3) *Robustness to mutations or misinterpretation*. Cellular sensors and the downstream processes could malfunction for various reasons, such as due to mutations. Such errors could have a significant impact if only true/false digital outcomes were allowed. However, binding interactions typically rely on multiple small contributions, so individual errors would have a small effect. Furthermore, it seems that extra robustness has sometimes been designed into the binding interactions as a buffer against future mutations while avoiding interactions being so strong that they are irreversible (Payne and Wagner, 2015; Aguilar-Rodríguez and Wagner, 2017).

4) *Permits use of simpler, dedicated processing machines*. Digital computers use general-purpose, very complex hardware. There are several reasons why using a variety of simpler, dedicated molecular machines makes more sense in the case of cells. These machines are involved in defining sensors, ensuring reliable interactions with signals, and implementing the downstream processes initiated by sensors.
- The variety of sensors and concentration gradients are built using unrelated media such as DNA, RNA, proteins, lipids, sugars, etc. A monolithic server that integrates all these components would be excessively complex.
- The copy number of dedicated molecular machines (e.g., aminoacyl-tRNA synthetases, ribosomes, spliceosomes, etc.) can be rapidly assembled just in time when needed and dismantled when no longer

Table III. Examples of cellular variables located on proteins and the bio-components involved.

Cellular process	Sensor	Sensing feature	Signal recognized by sensor	Quality control (QC) and stabilization (Stab) of sensor with signal	Complexes recruited during subsequent processes	References
Translocation of proteins in humans	Location of Signal peptide	~25–30 residue pattern at the N-terminal of proteins	Signal recognition particle (SRP), a ribonucleoprotein complex	QC: Proofreading by enhanced stimulation of GTP activity upon correct binding of signal peptide, SRP, and the SRP receptor (SR). Stab: Collaborative binding of Signal peptide, SRP, and SR.	Translocon complex; signal peptidase; several complexes to guide to the endoplasmic reticulum (ER), Golgi apparatus, lysosomes, or out of the cell.	Owji et al., 2018
MAPK/ERK signaling pathway	Extracellular ligand-binding location	Ig-like and EGF-like domains, fibronectin type III repeats, and cysteine-rich regions	Growth factors and mitogen ligands	QC: Ligand to receptor interactions include H-bonds, hydrophobic interactions, electrostatic forces, and van der Waals forces. Stab: Initial ligand binding usually promotes dimerization of receptor monomers. Also, co-receptors are often involved.	Adapter proteins (SOS and GRB2) are recruited, producing a cascade that changes gene expression.	Park et al., 2000; Cordover and Minden, 2020; Kumar and Hassan, 2023
Adenylyl cyclase signaling pathway	Location of extracellular G protein-coupled receptor (GPCR)	3 extracellular loops have distinctive amino acid sequences and shapes. Many GPCRs are glycosylated to provide unique features.	Regions of hormones, neurotransmitters, and odorants; photons	Stab: H-bonds, hydrophobic interactions, van der Waals forces, and ionic bonds.	Heterotrimeric G-protein, and adenylyl cyclase that produces cAMP (a second messenger), which activates protein kinase A, etc. leading to changes in gene expression, metabolism, and cell proliferation.	Dunn et al., 2019; Vidad et al., 2021
Immune defense against pathogens	Location of Complementarity Determining Region (CDR) on the antibody	Complementary sequence for antigen	Regions of antigen recognized	Stab: Non-covalent interactions, including hydrogen bonds, ionic bonds, van der Waals forces, and hydrophobic interactions between CDR and antigen.	A variety of complexes are then assembled that depend on the type of antibody	Osajima et al., 2014; Qu et al., 2021; Ghai et al., 2022
Gene regulation via the Histone Code	Location on H3, H4, H2A, and H2B	Pattern on lysine and arginine recognized by enzymes	The active site of enzymatic writers like HATs, HMTs, E3 ligases, kinases, Sumoylases, ARTs and PARPs	QC: Aberrant modifications could be removed by an eraser enzyme; kinetic proofreading. Stab: Cofactors; presence or absence of other modifications; targeting subunits that recognize specific features.	Recruitment of proteins containing "reader" domains, followed by assembly of Effector Complexes.	Turner, 2000; Arnold et al., 2011; DesJarlais and Tummino, 2016; Wagner et al., 2016

needed, recovering amino acids and nucleotides that can be used for other purposes. To clarify, up to ten million copies of ribosomes translate mRNA strands concurrently in human liver cells vs. none in red blood cells (Shore and Albert, 2022); up to 100,000–200,000 spliceosomes are active in many cell types concurrently (Garcia-Blanco, 2003); and ~75,000 polymerase II/III are active in many cell types

(Jackson et al., 1998). Capacity is adjusted taking into account cell type, stage in the cell cycle, and current cellular needs.

- Cells often use different versions of molecular machines for special purposes, such as those done by different spliceosomes (Mabin et al., 2021) and ribosomes (Chen et al., 2020). The proportion of these can be adjusted rapidly as needed.
- Using fewer components decreases the possible points of system failure.
- Defective parts can be easily replaced or repaired, for example, a damaged protein or RNA (Swovick et al., 2018; Yoon-Mo et al., 2023).
- Multiple copies of redundant critical components –including gene copies (Li et al., 2010) can be used, including preformed subassemblies for rapid ramp-up (D'Angelo et al., 2021) and to enhance overall cell robustness.
- Assembling complex monolithic cellular computing devices would not only be error-prone but also time-intensive. However, frequent disassembly of small processors and assembling new ones decreases the chance of wear and tear accumulating (e.g., through oxidation or misfolding of proteins, etc.).

Summary and Conclusions

We have emphasized that thousands of cellular sensors can respond to continuous changes in informative signals. The resulting sensor and signal interaction produces a microenvironment that recruits the necessary biochemicals in a series of regulated steps to provide useful processes. The assembly steps usually also generate new sensors, allowing optimal output to be regulated at several levels and to integrate many relevant factors about the current needs of a cell. This is an entirely different perspective than the chemistry-based notion that proteins and other biomolecules randomly happen to interact properly, perhaps after a few rounds of natural selection.

Cellular logic rarely displays the nature of digital programming. In cells, changes in the sensor's physical properties and signals modify the sensitivity of response, which is not how digital computing works. For example, in these assignment statements in digital programming

```
current_object = 'x'
kurrent_object = 'x'          (4)
```

there is no difference in the probability of being assigned the value of 'x.' Also, one cannot assume that physically more similar variables would lead to more similar outcomes.

In digital computing, the symbols are freely assignable and abstract. In cellular variables, distinct physical binding must occur. This might suggest that analog variables do not possess the key property of abstractness, that is, to be arbitrarily assignable to mean whatever a programmer wishes. Given the requirement of physical binding, might cellular processes be deterministic machines instead of computing devices? The answer is no, as explained by the concept of adaptors. A membrane receptor (sensor) must indeed recognize when a specific hormone has attached, but the abstract intention is revealed by the set of proteins thereby produced several steps later.

The abstract logic is not expressed in a separate source code, but is engineered into how the downstream activities will be judiciously assembled. Traced back to the sensor, small physical changes in the sensor properties will inevitably correlate with the processing outcome. Stated in another way, the abstract character of cellular variables is their ability to achieve useful goals that are unrelated to the physical binding properties used.

The intention of this 3-part series is to prepare the path to continue retro-engineering how cells function, in particular their ability to adapt, self-regulate, and reproduce autonomously.

An important intuition championed by creationist computer science professor Uwe Assmann in Germany is the concept of cellular metaprogramming. In computer science, this refers to the technique of simpler code being used to generate more complex executable code. This is relevant for our work, since clearly sensors on, for example, proteins were not present in the DNA genome, but were implicit and generated. Other examples of metaprogramming include sensors present on RNA (i.e., not on the DNA from which RNA arose) involved in chemical editing, intron-exon splicing, translation, gene regulation, RNA localization, RNA degradation rates, translation initiation strength, etc.

This series will prepare the groundwork for the concept of analog metaprogramming, whereby the necessary hardware and logic processing machinery are assembled by cells as needed.

Thousands of different programs execute concurrently in cells, usually with many copies of each. Through carefully engineered physical interfaces, these processes can execute autonomously as analog computing devices with little resemblance to digital computers and even less to natural chemical processes.

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