Computing with Competition in Biochemical Networks

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Cells rely on limited resources such as enzymes or transcription factors to process signals and make decisions. However, independent cellular pathways often compete for a common molecular resource. Competition is difficult to analyze because of its nonlinear global nature, and its role remains unclear. Here we show how decision pathways such as transcription networks may exploit competition to process information. Competition for one resource leads to the recognition of convex sets of patterns, whereas competition for several resources (overlapping or cascaded regulons) allows even more general pattern recognition. Competition also generates surprising couplings, such as correlating species that share no resource but a common competitor. The mechanism we propose relies on three primitives that are ubiquitous in cells: multiinput motifs, competition for a resource, and positive feedback loops.

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Biological cells process and respond to a myriad of signals [1–3]. For example, when bacteria are offered several sugars on which to grow, they select the sugar metabolism that yields the quickest growth and turn off unneeded sugar pathways [4].

Cellular decision pathways often compete for resources that are limited. For instance, on average 10 binding sites compete for each transcription factor in E. coli [5] and 40 in S. cerevisiae [6]; the archetypal enzymes of signal transduction—kinases—typically share docking proteins to transmit their signals [7]; during protein expression, cells have to parsimoniously allocate their ribosomes to competing mRNAs in order to sustain their proliferation [8,9].

It is difficult to apprehend competition because of its global nature: the addition of one substrate immediately slows down the processing of all the substrates that share the same resource. While the question of competition remains a puzzle for system and synthetic biologists [10–14], evolution has seamlessly integrated its effects into cellular pathways. This raises the intriguing possibility that the global coupling and nonlinearity provided by competition may be instrumental rather than detrimental to some cellular computations.

Alongside competition, positive feedback loops are common elements of biology [15–17]. For example, about 10% of transcription factors in E. coli positively regulate their own transcription [18]. Positive feedback may be direct, such as a kinase phosphorylating itself. But it may also be indirect and more subtle. For instance, the presence of a specific sugar inside a cell promotes the expression of the corresponding sugar transporter, which in turn leads to more of that sugar being transported inside the cell [4]. In development, some genes activate their own expression by first activating helping proteins in adjacent cells [19].

Kim, Hopfield, plus Winfree showed that, in biochemical systems, competition for a resource plus positive feedback generate a nonlinear effect known as winner-take-all (WTA) [20]. This effect amplifies the substrate that best exploits the resource and represses the others. A similar eviction effect in ecology is often summarized as complete competitors cannot coexist [21]. WTA behaviors have been observed in many complex systems with limited resources, such as the worldwide web, business, or citations networks [22].

WTA has been shown mathematically to be a powerful computational primitive. For instance, a single k-WTA (which amplifies the k strongest signals) offers the same computational power as a multilayer perceptron [23]. More generally, competitive neural networks—sets of neurons that compete to fire—are thought to underlie brain functions such as speech recognition [24,25].

In this Letter, we show how physical competition for a resource may be exploited by biochemical networks to process information. The work is motivated by the striking abundance of three particular elements in cellular pathways: multiinput motifs [6,26,27], positive feedback loops [7,15–17], and competition for a resource [10,11,13]. This observation naturally raises the question of whether a combination of these elements plays a specific function in cells. We show how competitive single-layer networks, such as sensory transcription networks [1], can recognize complex patterns despite their shallowness. We also illustrate how the global coupling of competition can correlate species without a common resource. This demonstrates that the absence of direct molecular interactions between nodes of a cellular network does not prevent the emergence of a global, integrated behavior.

We first develop a single-resource theory that explains how a unique winner emerges from a pool of competing species and how this leads to the computation of Boolean functions; we consider several output species $Y_j$, each promoting its own growth through a chemical process that requires a limiting and shared resource $R$. All other resources used for the growth of $Y_j$ are in large excess, so
we do not explicitly account for them. It is important to note that a resource here can be any chemical species that is limiting for the autocatalytic growth of \( Y_j \); it is not limited to the enzymatic catalysts of the process but also includes cofactors or even reagents. The outputs \( Y_j \) bind reversibly to the resource \( R \) to give a complex \( R:Y_j \), which ultimately leads to the production of more \( Y_j \). The binding of \( Y_j \) to \( R \) is usually much quicker (\( \sim 1 \) sec. for binding of a transcription factor [18]) than the production of \( Y_j \) (\( \sim 3 \) min. for the complete synthesis of a protein [18]). Therefore, \( R \) and \( Y_j \) are in equilibrium on the time scale of production of \( Y_j \), and we have

\[
R + Y_j \leftrightarrow R:Y_j, \quad [R:Y_j] = [R][Y_j]/K_j. \tag{1}
\]

The total concentration \( R^0 \) of the resource is constant, either because it is not consumed (catalytic reactions) or because it is replenished continuously. Conservation of the resource and Eq. (1) give

\[
[R:Y_j] = \frac{R^0 Y_j}{1 + \sum_i Y_i/K_i}. \tag{2}
\]

Competition appears quantitatively in Eq. (2): the addition of an output \( Y_j \) immediately decreases the concentration of other complexes \( [R:Y_k] \).

Following classic regulatory design, we now consider a set of cellular or environmental signals \( X_i \) that modulate the production of \( Y_j \) by interacting—directly or indirectly—with the complex \( R:Y_j \). For example, membrane sensors transduce physical signals (oxidative stress, thermal shocks, etc.) or biochemical signals into transcription factors [3] or phosphorylated proteins [28], which eventually mount a cellular response, e.g., by altering the level or activity of appropriate enzymes. An input function \( f_j(X) = k_j(X)/K_j \) encodes how the inputs modulate the production of \( Y_j \) by \( R:Y_j \),

\[
R:Y_j \xrightarrow{k_j(X)} R + 2Y_j.
\]

Finally, outputs \( Y_j \) decay, for instance through degradation or dilution (proteins’ half-lives are from dozens of minutes to hours [29]). Dilution is a first-order process, affects all species similarly, and prevails over degradation in rapidly dividing cells such as bacteria in exponential growth. Enzymatic degradation is species-specific, prevails over dilution in slow or nondividing cells, and follows saturable kinetics [29,30]. Saturable but noncompetitive degradation may introduce hysteresis because it biases competition in favor of species with large initial concentrations. Nevertheless, we find that saturable degradation does not qualitatively change the WTA when outputs also compete for degradation (Sec. 8 in Supplemental Material Ref. [31]). Here, we assume for simplicity a globally first-order decay; i.e., the degradation pathways are not saturated. The overall kinetics for a given \( Y_j \) are given by adding its rates of production and decay,

\[
\dot{Y}_j = -k_j(X)Y_j - \beta_j Y_j - \frac{f_j(X)R^0 Y_j}{1 + \sum_i Y_i/K_i} - \beta_j Y_j, \tag{3}
\]

The production rate varies linearly with \([R:Y_j]\), which implies that there is no saturation of the resources used downstream of \([R:Y_j]\). The production rate of \( Y_j \) is analogous to classical Michaelis–Menten kinetics: it is proportional to \( Y_j \) at low concentrations but saturates for concentrations much larger than \( K_j \). Such saturation, ubiquitous in enzyme dynamics, is characteristic of processing by a limiting resource.

At the steady state \( \dot{Y}_j = 0 \), which can be rewritten as

\[
Y_j^\infty = 0, \quad \text{or} \quad \frac{\beta_j}{f_j(X)} = \frac{R^0}{1 + \sum_i Y_i^\infty/K_i} = R^\infty. \tag{4}
\]

The amount of free resource \( R^\infty \) adjusts to balance production and decay. If a single output \( Y_j \) uses \( R \), the dynamics are trivial and lead to a steady state \( Y_j^\infty = K_j\left(\frac{f_j(X)}{\beta_j} - 1\right) \), assuming production can compensate decay.

WTA occurs when several outputs compete for the resource \( R \). As can be seen in Eq. (3), an increase in one output \( Y_j \) accelerates its growth while it decelerates the growth of all other outputs. An imbalance in growth snowballs to such extent that, at the steady state, one of the outputs monopolizes the resource (but most of the resource can still be free; Sec. 2 in Supplemental Material Ref. [31]). In any case, the losing outputs disappear due to their continuous decay. Indeed, let us assume that two outputs \( Y_j \) and \( Y_k \) survive at the steady state, \( Y_j^\infty > 0 \) and \( Y_k^\infty > 0 \). Then we can deduce from Eq. (4) that \( \beta_j/f_j(X) = \beta_k/f_k(X) \). This perfect equality is not physically realistic: any infinitesimal difference between the two quantities will eventually produce the WTA. Thus, at most one output survives at the steady state because the free resource \( R \) can only balance the rate of production and decay of a single output. We show in Sec. 1 in the Supplemental Material that the only stable output \( Y_j^\infty \) is the one that minimizes \( \beta_j/f_j(X) \) and thus the concentration of free resources at the steady state [31].

Let us summarize the computation of the winner-take-all networks. A layer of input \( X_i \) modulates the growth of outputs \( Y_j \) that compete for a limiting resource \( R \). Competition leads to a winner-take-all effect that amplifies the single most efficient output and eliminates the others. The result of the computation is given by the surviving output at the steady state, which depends on the modulation of the inputs. The following formula recapitulates the dynamic:

\[
Y_j^\infty = \begin{cases} 
K_j\left(\frac{R^0 f_j(X)}{\beta_j} - 1\right), & \text{if } j = \arg\min_k \frac{\beta_j}{f_j(X)}, \\
0, & \text{else}
\end{cases} \tag{5}
\]

In the context of cellular signal processing, WTA is a perfect primitive to compare stimuli and coordinate
pathways that need not respond simultaneously, such as those that metabolize sugars in E. coli [4]. WTA may also help to select cellular species that maximize a given fitness function, similarly to clonal competition where the immune system uses competition to maximize the affinity of B cells [32].

The computation performed by the network is encoded within the input function $f_j(X)$. For the rest of the Letter and for the sake of simplicity, we assume that inputs linearly modulate the activity of $R_j$:

$$f_j(X) = \frac{k_j(X)}{K_j} = \alpha / K_j \max \left( \sum_i w_{ij} x_i / K_j, 0 \right).$$

The max ensures that rates are positive, a requirement for chemical production rates. We now illustrate how competition allows winner-take-all networks to recognize complex patterns despite the simplicity of $f_j(X)$.

The WTA networks resemble a perceptron with their single-layer architecture. Yet they are much more powerful because of the global and nonlinear nature of competition. Unlike the perceptron, they compute Boolean functions that are not linearly separable because competition allows the recognized set of inputs to be bounded [33].

This is illustrated in Fig. 1. The network in Fig. 1(a) computes a linearly separable function, a NAND. The nature of the computation changes when an additional output $Y_4$ competes for $R$. A similar structure (bi-fan) is common in transcription and kinase networks [27]. The range of inputs for which $Y_2$ wins is now bounded, implementing a XOR [Fig. 1(b)].

Competition offers cells the same computational power as a perceptron [e.g., NAND in Fig. 1(a)], without requiring large Hill coefficients, hence, the formation of higher-order molecular complexes [18]. Competition is even more powerful and generates outputs which vary nonmonotonically with their inputs [e.g., XOR in Fig. 1(b)], which may explain intriguing nonmonotonic behaviors observed experimentally [4]. Yet, a single pool of resource cannot compute a NOT XOR, as the winning domain of an output must be convex (Sec. 4 in Supplemental Material Ref. [31]).

Directly cascading two WTAs allows for the computation of a NOT XOR and, thus, of any two-input Boolean function. In Fig. 1(c), $Y_2$ performs an XOR in the $R_a$ pool and is also an activating input for $Y_3$ in the $R_b$ pool. Output $Y_4$ wins in the $R_b$ pool only if $Y_2$ does not win in the $R_a$ pool, implementing a NOT XOR. Such cascaded architectures are common in development networks [18].

Competition is known to correlate species sharing a degradation resource when they fluctuate around a balancing point (correlation resonance, [10,11]). Surprisingly, we show that competition even couples species without a common resource, provided they share a common competitor. Figure 2 shows such overlapping pools of resource: $Y_2$ uses two resources, $R_a$ and $R_b$, in parallel to grow, while $Y_1$ or $Y_3$ can only use one of these. A similar regulation architecture (dense overlapping regulons) is widespread in sensory transcription networks [1,27]. The weights fluctuate randomly around their mean value. When the mean weights are balanced, $\langle w_{0j}^{a} \rangle + \langle w_{0j}^{b} \rangle = \langle w_{i0}^{a} \rangle = \langle w_{i0}^{b} \rangle$, outputs become suddenly correlated [corr($Y_1, Y_3') = 0.96$ in Fig. 2(a)]. Indeed, for $Y_2$ to lose, $Y_1$ and $Y_3$ must win simultaneously, a condition which strongly correlates the three species. Competition also amplifies fluctuations: while the weights fluctuate by only 10% around their mean, the outputs fluctuate by 70% [34]. These indirect

![FIG. 1 (color online). Computation of Boolean functions. (a) A NAND. The plot shows the level of $Y_j$ at $t = 20/\beta$, as a function of the inputs. The winner of each domain is indicated on the plot. (b) Addition of a competitor $Y_3$ turns the linearly separable NAND into a nonlinearly separable XOR. (c) Computation of a NOT XOR by directly connecting two WTAs. Weights are given in Supplemental Material [31].](image)

![FIG. 2 (color online). Overlapping pools of resources. (a) Competition correlates the fluctuations of outputs that share no resource but a common competitor. The plot shows the time course of the outputs' fluctuations, for the balanced regime $\langle w_{0j}^{a} \rangle + \langle w_{0j}^{b} \rangle = \langle w_{i0}^{a} \rangle = \langle w_{i0}^{b} \rangle$. Weights $w_{0j}$ are independently drawn from a log-normal distribution with constant mean and s.d. every $\Delta t = 2/\beta$. (b) Computation of a NOT XOR with overlapping pools of resources. The function computed by $Y_2$ in each pool is indicated close to this pool. The plot shows the level of $Y_j$ at $t = 20/\beta$, as a function of the inputs.](image)
connections between outputs highlight the subtle and indirect coupling introduced by competition, as noted in neuronal networks [25]. From a Boolean logic perspective, the overlapping pools can also compute a NOT XOR within a single layer, since \( Y_2 \) computes an OR between the two pools [Fig. 2(b)]. This additional computing power provided by overlapping but single-layer architectures may account for their prevalence in transcription networks.

We now consider a detailed model of transcription in which pools of proteins (regulons) compete for transcription factors [Fig. 3(b)]. We kinetically model transcription as a four-step mechanism that requires the sequential binding of a single resource, since the promoters pool [Fig. 2(b)]. This additional computing power provided by overlapping but single-layer architectures may account for their prevalence in transcription networks.

We choose kinetic and thermodynamic parameters typical of prokaryotes such as *E. coli* [18,35,36].

While this three-resources model is analytically intractable, we may apprehend limit cases with our single-resource theory. The key point is to note that among the three types of resource (pooled, individual, and global), one will usually be limiting and determine the scale or existence of competition [37]. If \( TF_k^n \ll K_D \), the dimer \( Y_j \); \( TF_k \) never saturates its promoter because \( [Y_j;TF_k] \leq TF_k^n \ll K_D \), and promoters are mostly free. Intuitively, \( TF_k \) is a bottleneck resource for \( Y_j \). Competition takes place within the regulon for \( TF_k \), and our theory predicts that a single winner emerges from this regulon. On the other hand, if \( TF_k^0 \gg K_D \), then promoters readily saturate and become the bottleneck resource for \( Y_j \); \( TF_k \). Since outputs do not compete for their promoters, all outputs coexist. In these two limit cases, polymerase is not a bottleneck and thus we do not expect a global competition between regulons for the polymerase. Additionally, competition between promoters for the polymerase would be inefficient, as the former can hardly saturate the latter (\( D_k^0/K_P = 0.2 \)).

Figure 3 presents two regulons that recognize—in parallel—patterns that are not linearly separable (Sec. 7.1 in Supplemental Material Ref. [31]). The concentrations of TF in the regulons span the physiological range (1–1000 nM [36]) and illustrate the limit cases presented above (high and low \( TF_k^0/K_D \)). Figure 3(d) numerically confirms that \( TF_k^0/K_D \) qualitatively predicts the scale and magnitude of competition. In regulon \( TF_1 \) (\( TF_1^0/K_D = 0.02 \)), an unambiguous winner emerges for each pattern. In the regulon \( TF_2 \) (\( TF_2^0/K_D = 20 \)), several or all outputs coexist with concentrations of similar magnitudes. The classification performance of regulon \( TF_1 \) gracefully degrades with noise; it still recognizes 60–90% of patterns in the presence of a frozen, multiplicative noise of 50% on its weights (Fig. 3(c); Sec. 7.2 in Supplemental Material Ref. [31]).

A notable feature of bacterial transcription networks is the relative absence of cascades between their inputs and outputs [1,18,27]. This shallowness presumably allows bacteria to respond quickly to environmental changes. However, such single-layer networks compute a limited range of functions, unless they resort to complex ad hoc interactions between inputs or outputs [36]. We have shown that competition, which has been seldom addressed in the literature, imparts greater nonlinear computational power to single-layer networks.

Eukaryotes display a wealth of mechanisms that may modulate the spatial and temporal scales of competition. For instance, competition may be localized by cellular compartments [38] or generalized by intercellular communication [39,40], allowing local or global winners to emerge. Transport of transcripts and proteins through the nucleus produces delays and may lead to oscillations [41], preventing the emergence of a stable winner [37]. Cooperativity—because it introduces higher-order processes and hysteresis—may extend the temporal scale.
of competition further into the past and enable memories [42, 43].

The existence of effects arising from molecular competition raises the need to appreciate the importance of global coupling. Our work suggests that cells may use competition between proteins that have no direct interactions to exchange information on a global level. For instance, coexpression of two genes is often taken as a clue that they share a common transcription factor [44], but recent studies have called this view into question for complex species [45]. Competition could well correlate the expression of two genes that do not share any transcription factor if their regulons overlap, as suggested by Fig. 2(a). The global coupling induced by competition among molecules may allow cells to synchronize pathways, commit to decisions, and select species with maximal fitness, while using few molecular connections.

In conclusion, rather than being detrimental as generally assumed, physical competition for a resource may be exploited to process information in biochemical networks. We have given examples of how cells may use the non-linearity of competition to compute complex functions and its globality to coordinate antagonist pathways. The parallel between competition in molecular and ecological systems [42] suggests that cellular pathways may be ecosystems unto themselves, with entangled dynamics of growth, decay, and competition [9].

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[33] A Boolean function is linearly separable if the combinations of inputs that give a TRUE result can be separated by a plane from the combinations of inputs that give a FALSE result.
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