

On Bioelectric Algorithms

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Abstract

Cellular bioelectricity describes the biological phenomenon in which cells in living tissue generate and maintain patterns of voltage gradients across their membranes induced by differing concentrations of charged ions. A growing body of research suggests that bioelectric patterns represent an ancient system that plays a key role in guiding many important developmental processes including tissue regeneration, tumor suppression, and embryogenesis. This paper applies techniques from distributed algorithm theory to help better understand how cells work together to form these patterns. To do so, we present the cellular bioelectric model (CBM), a new computational model that captures the primary capabilities and constraints of bioelectric interactions between cells and their environment. We use this model to investigate several important topics from the relevant biology research literature. We begin with symmetry breaking, analyzing a simple cell definition that when combined in single hop or multihop topologies, efficiently solves leader election and the maximal independent set problem, respectively – indicating that these classical symmetry breaking tasks are well-matched to bioelectric mechanisms. We then turn our attention to the information processing ability of bioelectric cells, exploring upper and lower bounds for approximate solutions to threshold and majority detection, and then proving that these systems are in fact Turing complete – resolving an open question about the computational power of bioelectric interactions.

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1 Introduction & Related Work

An exciting emerging field in cellular biology is the study of *bioelectricity* [17, 25, 22]. This paper applies techniques from distributed algorithm theory to help advance these efforts.

Bioelectricity describes the patterns of voltage differentials caused by differing concentrations of charged ions inside and outside of a cell’s plasma membrane. Compelling new lab research, influenced by computer science’s use of abstractions, is revealing that these bioelectric patterns can in some cases play the role of high-level programming languages, providing a “biocode” that can specify goal states for cellular development that are then implemented by complex lower-level processes (see [25] for a recent survey).



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In this paradigm, altering a bioelectric pattern – e.g., using interventions such as chemical blockers that modify ion flux, or inserting membrane channels – is like altering the source code of a computer program, providing a mechanism for controlling how an organism develops. The ability to manipulate these processes at a high level of abstraction enables potentially massive breakthroughs in many different important areas, including organ and limb regeneration, tumor suppression, and powerful new forms of synthetic biology.

1.1 Opportunity

The key to unlocking the power of bioelectricity is understanding how the underlying *bioelectric networks* (BENs) interact to form patterns and process environmental input. To date, biologists have primarily studied these questions by describing specific BEN configurations as a system of differential equations, and then studying their behavior using analytical simulation. This provides only observational – *not expository* – insight into bioelectricity dynamics.

In this paper, we explore another investigatory approach that can yield powerful new understanding: the biological algorithms approach [30, 29]. By treating a given BEN configuration as a distributed algorithm running in a well-defined distributed system model, we can apply the tools of distributed algorithms to prove results about a network’s behavior, identify network designs that solve specified problems, produce lower bounds and impossibility results, and even assess the general computational power of the setting in question.

To do so, we begin in Section 2 by describing and motivating the *cellular bioelectric model* (CBM), a new computational model, designed in consultation with biologists who directly study these phenomena, that abstracts important capabilities and constraints of real world cellular bioelectrical networks. This model assumes a collection of *cells*, which are connected in a network topology that describes which cell pairs can directly interact (e.g., through ligand signaling). To simplify the model, time proceeds in synchronous rounds. The state of each cell at the beginning of a round is captured by a single value that describes the voltage *potential* across its plasma membrane. A *gradient* parameter captures the rate at which this potential increases or decreases toward an equilibrium due to ion flux through ion channels in its membrane.

Cells can communicate and compute through *bioelectric events*, in which a cell can induce a sudden increase or decrease to its potential (e.g., by pumping ions in/out, or opening/closing ion gates), and release aionic ligand molecules that can induce a sudden potential changes in its neighboring cells in the network topology. For each cell, and each bioelectrical event, a probability function specific to that event maps the cell’s current potential to the probability of the event firing. To maintain biological plausibility, our model requires that these probability function are monotonic, and allows each cell definition to include only a constant number of distinct bioelectric events.

Though the core computational process in the CBM – the *cell* – is quite simple and restricted, we are able to show that they are well-suited to exactly the types of distributed computational tasks that researchers now attribute to bioelectric behavior. Below we summarize our results and emphasize the concrete connections they form to active areas of biological inquiry.

1.2 Our Results: Symmetry Breaking

One of the key open problems in cellular bioelectrics is understanding the stochastic processes that allow otherwise identical cells to distinguish themselves into set patterns. We study these symmetry breaking tasks in Section 3, focusing in particular on the *KnockBack* cell

definition (see Section 3.1). This definition captures one of the simplest possible symmetry breaking strategies. Cells start with a low potential that gradually increases toward a higher equilibrium. As a cell's potential increases, it passes through a *competition* range in which, with constant probability, it fires a bioelectric event that bumps up its potential and emits a ligand that will reduce the potential of nearby cells. If it makes it through the competition range, its potential is high enough that the cell begins firing with probability 1 until it reaches a threshold after which it can begin a morphological transformation into a leader.

Though simple, **KnockBack** turns out to be an effective symmetry breaker. In Section 3.2, we study this strategy in a single hop (i.e., fully connected) network topology. We prove that not only does it safely elect a single cell to be leader, it does so in only $O(\log(n/\epsilon))$ rounds, with probability at least $1 - \epsilon$, where n is the network size. For high probability (i.e., $\epsilon < 1/n$), this bound is *faster* than the $O(\log^2 n)$ -round algorithm from a recent study of symmetry breaking with constant-size state machines [21]. It also matches the optimal $\Theta(\log n)$ bound on leader election with unrestricted state machines under the comparable network assumptions of a shared communication channel and collision detection [31].

In Section 3.3, we turn our attention to the behavior of **KnockBack** in connected multihop networks that satisfy the natural unit ball graph constraints [23] (which requires the topology to be compatible with the embedding of the cells in a reasonable metric space). In this setting, we consider the *maximal independent set* (MIS) problem, in which: (1) every cell must either become a leader or neighbor a leader; (2) no two neighbors are leaders. Our consideration of the MIS problem is not arbitrary. A 2011 paper appearing in the journal *Science* [4] conjectures that nervous system development in flies solves the MIS problem on a layer of epithelial cells to evenly spread out sensory bristles, motivating the investigation of biologically plausible strategies for solving this classical problem (c.f., [2, 33]).

We show, perhaps surprisingly, that the simple **KnockBack** strategy turns out to provide an effective solution to the MIS problem as well. In more detail, we prove that with high probability in the network size n , it establishes a valid MIS in at most $O(\text{polylog}(\Delta) \log n)$ rounds, where Δ is the maximum degree in the network (which in many biological settings, such as in [4], is likely a small constant).

Equally important for the study of bioelectrics, we show this strategy to be self-stabilizing. Even if you start each cell at an arbitrary initial potential, the system will efficiently stabilize to a valid MIS. The strategy is unique in that it requires only a single constant probability value in its definition, as opposed to the $\log n$ distinct probabilities used in most existing efficient solutions, including those proposed in existing biological distributed algorithm papers [4, 2, 33].

Given these powerful properties of the **KnockBack** strategy, plus a simplicity in design that makes it an easy target for natural selection to identify, we argue that it represents a reasonable (testable) hypothesis that bioelectric mechanisms might be drive these symmetry breaking tasks in real cellular systems.

1.3 Our Results: Information Processing

Another previously mentioned key open problem in cellular bioelectrics is understanding the capacity of cells to process information using bioelectric interactions. One conjecture is that simple interactions of the type captured in the CBM are not capable of much more than simple pattern generation (e.g., generating an MIS with **KnockBack** cells). A competing conjecture is that these interactions are actually capable of performing a wide variety of non-trivial computation.

In this paper, we use the CBM to provide support for the latter view of biological reality. We begin in Section 4 by studying *input type* computation, a simple form of information processing also studied in the biologically-plausible population protocol and chemical reaction network models (see model comparison below). In input type computation, the goal is to compute an output based on the *number* of cells in the system of one or more designated types. Two classical problems of this type are *threshold detection* [5], which computes whether the number of *sick* cells in the system is beyond a fixed threshold k , and *majority detection* [7], which computes whether there are more A cells than B cells in the system.

We study threshold detection in Section 4.1. For small thresholds, we present a simple cell that solves the problem exactly with no error.¹ For larger thresholds, we present a cell definition that for any error ϵ , correctly detects that the threshold is exceeded if the count n is greater than $k\tau$, and correctly detects that it is not exceeded if $n < k/\tau$, for $\tau = O(\log(1/\epsilon))$. We conclude by proving that *any* solution that works for general k values must have a non-zero error probability, regardless of how large we allow τ to grow.

In Section 4.2, we turn our attention to majority detection. We provide symmetric cell definitions for type A and B cells. For any constant error bound $\epsilon > 0$, these cells will correctly detect the majority type with probability $1 - \epsilon$ so long as there is a sufficiently large constant factor more of the majority type (for a constant factor defined relative to $\ln(1/\epsilon)$).

The general threshold detection solution is straightforward: cells send a ligand with probability $1/k$, and associate any received ligands with an exceeded threshold. The majority detection solution has cells increase the firing probability of a bioelectric event from a small lower bound to a constant as their potential increases towards equilibrium: whichever cell type fires first is assumed to be the majority type. In both cases, more refined probabilistic analysis would likely lead to tighter bounds, but the solutions and lower bound in Section 4 are sufficient to support the conjecture that bioelectric interactions can approximate standard input type computations (albeit it only probabilistically).

Finally, in Section 5 we consider a more general form of information processing, in which the input value to be processed in a given execution is encoded in the initial value of one or more designated input cells (for some encoding scheme specified by the designer of the cellular system). Understanding the set of functions that can be computed by such systems provides insights into the computational power of bioelectrics. With this motivation in mind, we prove, perhaps surprisingly, that bioelectric cells are Turing Complete. In slightly more detail, we prove that for any deterministic Turing machine (TM) M , there exists a finite collection of cells including a designated *input cell*, connected in a single hop network, such that for any TM input w , if you set the initial potential value of the input cell to a proper encoding of w , the system will correctly simulate M on w . Of course, one of the TMs that can be simulated is a universal TM, indicating the existence of a computationally universal collection of bioelectric cells.

1.4 Comparison to Existing Models

Generally speaking, in studying the intersection of biology and algorithms there are two main types of computational models used: those with *bio-plausible computation* and those with *bio-plausible constraints*. The first category describes models in which the actual method of computation is motivated by a specific biological context. Algorithms in these models

¹ In this context, “small” means that k is smaller than the maximum number of different ligand counts a cell can distinguish, allowing the cell to directly count the sick cells (see the definition of *binding bound* from Section 2).

cannot simply be described in standard pseudocode or state machine descriptions. They must instead be specified in terms of the particular bio-plausible computation method captured by the model. Well-known models of this type include neural networks [32, 36, 27, 26], chemical reaction networks [37, 12, 11], and population protocols [5, 8, 7, 9, 6, 10] (which are computationally equivalent to certain types of chemical reaction networks).

The other type of model used to study biological algorithms are those with bio-plausible constraints. These models describe computation with the same standard discrete state machine formalisms assumed in digital computers. They constrain algorithms, however, by adding biologically-motivated limits on parameters such as memory size, the message alphabets used for communication, and the behavior of the communication channels. Well-known models of this type includes the ANTS model [19, 24, 13, 20, 35], the stone age computing model [18], and the beeping model [16, 15, 28, 14, 1, 34, 3, 21].

Both models are useful for applying algorithmic tools to understanding biological systems. The bio-plausible computation models focus more on understanding the low level processes behind particular behaviors, while the bio-plausible constraints models focus more on identifying general distributed strategies, and understanding the minimum resources/assumptions required for useful distributed coordination.

The CBM is most accurately categorized as a bio-plausible computation model. Existing studies of the stone age and beeps computing models already shed light on what can be computed by collections of simple state machines with basic signaling capabilities. The goal here is to understand what can be computed with the *specific* bioelectric mechanisms implemented in living tissue. This goal is important as our work is designed to be relevant to system biologists that are studying and manipulating these specific mechanisms.

1.5 Cells vs. Neurons

There are interesting connections between the CBM and artificial neural network models. The action potential that drives neural computation is itself a bioelectric mechanism. Indeed, many of the basic artificial neural network models can be implemented as special case of our general CBM. The recent work in bioelectricity that motivates the CBM, however, deals with bioelectric activity outside of the neural context, which changes the relevant challenges. In neural networks, for example, the “algorithm designer” gets to carefully construct the network topology and precisely calibrate each cell (i.e., determine their exact connection weights). In the non-neural contexts that motivate this work, by contrast, the network topologies are either simple (single hop) or *a priori* unknown to the computing cells (an arbitrary multihop graph), and because pattern formation is a key behavior in this context, the focus is often on initially identical cells that break symmetry stochastically. In other words, though the CBM networks we study use similar underlying chemical mechanisms as neural networks, their behaviors are strongly distinguished.

1.6 Cells $\neq$ State Machines

A key factor differentiating the CBM from existing bio-plausible constraint models is that the cell formalism is computationally incomparable to a traditional state machine. Consider a basic task such as outputting a repeated pattern: `ABCABCABC...`. This is trivial for a discrete state machine: cycle through three states, one for each output symbol. It is not hard to show, however, that this behavior cannot be implemented by a cell in the CBM. The key difficulty is the required monotonicity for firing functions driving bioelectric events (which is an important property of the real biological cells being modelled). A simple argument

establishes that for any cell, there must be at least two symbols $S_1, S_2 \in \{A, B, C\}$, such that whenever S_1 has a non-zero probability of being output, so does S_2 – eliminating the possibility of perfectly repeating pattern. At the same time, we cannot necessarily simulate an arbitrary cell with a finite state automaton either, since each cell stores an analog and unbounded potential value. It is therefore unclear how to use an existing bio-plausible constraint model to directly explore bioelectric dynamics – directly modeling the bioelectric dynamics seems necessary for understanding these systems.

1.7 Why Study This Model?

A shortcoming of the biological algorithms approach is that it can spawn an unlimited number of new models. The difficult question for advancing this field is identifying *which* models are actually worth ongoing examination. In defense of the CBM, we note that it was created in response to interactions with biologists who were excited about the potential of bioelectricity and increasingly comfortable borrowing ideas from computer science. The details of the CBM presented here were identified in consultation with these biologists, and the initial problems we study were directly motivated by questions in the existing literature. Even so, we made several modelling decisions that can be questioned (e.g., regarding both fidelity and tractability), and only future attempts to use the CBM to better understand biology will help to resolve those questions. Successful synthesis of algorithm theory and biology is an exceedingly hard endeavor, but we contend that this direction is well-motivated.

2 The Cellular Bioelectric Model

Here we define the cellular bioelectric model (CBM), a synchronous computation model that abstracts the key capabilities and constraints of bioelectric networks.

2.1 Biology Background

A bioelectric network describes the bioelectric properties of a collection of cells in some well-defined space. The key property describing the network is the net difference in charged ion concentration between the inside of each cell and the extracellular environment. There are two main mechanisms by which the voltage across a given cell's plasma membrane can change. The first is charged ions moving in or out of membrane channels driving the cells interior ion concentration toward equilibrium with the outside extracellular environment. The second mechanism is ligand signalling. A given cell's voltage can induce the release of special signalling molecules called ligands into the extracellular environment. These ligands can then bind to receptors on nearby cells, either opening channels in the receiver's membrane or activating ion pumps, rapidly changing the ion concentration of the receiver. The release of ligands by the cell can also cause a sharp change to its own ion concentration through similar mechanisms. These bioelectric events are stochastic in nature with a probability that seems to depend monotonically on a cell's current voltage; e.g., the probability of an event either becomes increasingly more or less likely as the voltage grows.

The below model captures the core properties of these dynamics. The voltage of each cell is captured by a single analog *potential value*, while we capture the passive drive toward equilibrium with both an equilibrium value and a rate at which each cell's potential drives toward that equilibrium. Bioelectric events are described by probability functions that map cellular potential values to the probability of the event firing. Finally, we use a graph to describe the cellular topology, where an edge (u, v) means that the cells corresponding to u and v are within ligand signalling range.

By necessity, this model simplifies the real biology in several important ways. For example, our discrete bioelectric events actually approximate analog non-linear responses to signaling, and likely limit the full range of signalling interactions possible in real systems. In addition, we consider only anionic ligands (no charge), whereas some well-known bioelectric interactions seem to rely on cationic ligands that change the charge of the extracellular environment. Also notable, for the sake of simplicity, we omit the inclusion of *gap junctions*, which are direct channels between cell pairs that can open and close in response to the voltage gradient induced by their endpoints.

2.2 Cells

Fix a non-empty and finite set L containing the *ligands* cells use to drive bioelectrical interactions. We define a *bioelectric event* to be a pair $(f, (\delta, s))$, where $f : \mathbb{R} \rightarrow [0, 1]$ is a *firing function* from real numbers to probabilities, and (δ, s) consists of a *potential offset* value $\delta \in \mathbb{R}$, and a *ligand* $s \in L$. We also define a *membrane function* to be a function g from multisets defined over L to real numbers.

Pulling together these pieces, a *cell* in our model is described by a 6-tuple $(q_0, \sigma, \lambda, \omega, g, \mathcal{B})$, where $q_0 \in \mathbb{R}$ is the *initial potential* value of the cell, $\sigma \in \mathbb{R}$ is the *equilibrium* potential that the cell will drive its internal potential toward (i.e., through ion flux), $\lambda \in \mathbb{R}^+$ is a non-negative real number describing the *gradient* rate at which the cell's potential moves toward σ , $\omega \in \mathbb{R}$ is the smallest possible potential for the cell, g is a membrane function, and $\mathcal{B}$ is a set of bioelectric events. For a given cell c , we use the notation $c.q_0, c.\sigma, c.\lambda, c.\omega, c.g, c.\mathcal{B}$ to refer to these six elements of the cell's tuple.

2.3 Systems and Executions

A *system* in our model consists of a non-empty set $\mathcal{C}$ of $n = |\mathcal{C}|$ cells, an undirected graph $G = (V, E)$ with $|V| = n$, and a bijection $i : \mathcal{C} \rightarrow V$ assigning cells to graph vertices. For simplicity, in the following we sometimes use the terms *cell* u or *node* u , for some $u \in V$, to refer to the unique cell $c \in \mathcal{C}$ such that $i(c) = u$.

An *execution* proceeds in synchronous rounds that we label $1, 2, 3, \dots$. At the beginning of each round r , we define the *configuration* $C_r : \mathcal{C} \rightarrow \mathbb{R}$ as the bijection from cells to their potential values at the beginning of round r . For each $c \in \mathcal{C}$, $C_1(c) = c.q_0$. That is, each cell starts with the initial potential value provided as part of its definition. The configuration for each round $r > 1$ will depend on the configuration at the start of round $r - 1$, and the (potentially probabilistic) behavior of the cells during round $r - 1$.

In more detail, each round $r \geq 1$ proceeds as follows:

1. For each cell $c \in \mathcal{C}$, initialize $p_c \leftarrow C_r(c)$ to c 's potential at the start of round r . We will use p_c to track how c 's potential value changes during this round. Also initialize multiset $M_c = \emptyset$. We will use M_c to collect ligands sent toward c during this round.
2. For each cell $c \in \mathcal{C}$, and each bioelectric event $(f, (\delta, s)) \in c.\mathcal{B}$, this event *fires* with probability $f(C_r(c))$. If the event fires, update $p_c \leftarrow p_c + \delta$ and add a copy of s to multiset $M_{c'}$, for each cell $c' \in \mathcal{C}$ such that $\{i(c), i(c')\} \in E$ (that is, for each cell c' that neighbors c in G).
3. After processing all rules at all cells, the round proceeds by having cells process their incoming ligands. For each cell $c \in \mathcal{C}$, update $p_c \leftarrow p_c + c.g(M_c)$. That is, update the potential change according to c 's membrane function applied to its incoming ligands.

4. Finally, we calculate the impact of the gradient driving each cell c 's potential toward its equilibrium value. In more detail, let $z = C_r(c) - c.\sigma$. We define the gradient-driven potential change for c in round r , denoted $\lambda_r(c)$, as follows:

$$\lambda_r(c) \leftarrow \begin{cases} -c.\lambda & \text{if } z \geq c.\lambda \\ -z & \text{if } 0 < z < c.\lambda \\ 0 & \text{if } z = 0 \\ z & \text{if } -c.\lambda < z < 0 \\ c.\lambda & \text{if } z \leq -c.\lambda \end{cases}$$

We add this gradient-induced offset to c 's potential: $p_c \leftarrow p_c + \lambda_r(c)$.

5. The final step is to the initial potential for $r + 1$ for each $c \in \mathcal{C}$, by performing a final check that the potential did not fall below the cell's lower bound in the round: $C_{r+1}(c) \leftarrow \max\{p_c, c.\omega\}$.

2.4 Natural Constraints on Cell Definitions

To maintain biological plausibility, our model includes the following natural constraints on allowable cell definitions:

- *Constraint #1:* Each cell definition includes at most a constant number of bioelectric events.
- *Constraint #2:* Firing functions are monotonic.
- *Constraint #3:* For each membrane function g , there must exist some constant $b > 0$, such that for every possible ligand multiset M , $g(M) = g(\hat{M})$, where $\hat{M}$ is the same as M except every value that appears *more* than b times in M is replaced by exactly b copies of the value in $\hat{M}$. We call the value b the *binding bound* for that cell definition.

2.5 Expression Events & Thresholds

In real biological systems, bioelectric patterns induce morphological changes driven by lower-level processes. To capture this transformation we introduce the notion of *expression events* into our model (named for the idea that bioelectrics regulates gene *expression*).

In more detail, some of our problem definitions specify a potential threshold such that if a cell's potential exceeds this threshold, an irreversible morphological transformations begins. This occurs at the beginning of each round, i.e., if a cell begins round r with a potential that exceeds the event threshold, we apply the event. For example, in studying leader election (see Section 3), we assume once a cell passes a given threshold value with its potential it transforms into a *leader*, at which point it stops executing its original definition and transforms neighbors that have potential values below the threshold into *non-leaders*. The specification and motivation for specific expression thresholds are included as part of the problem definitions.

3 Symmetry Breaking

A fundamental task in bioelectric networks is generating non-trivial bioelectric patterns that can then direct cellular development. This requires symmetry breaking. With this in mind, we study the symmetry breaking capabilities of a natural, but surprisingly effective, cell called **KnockBack**. We summarize its ability to elect a leader in single hop networks, and to efficiently generate maximal independent sets in multihop networks.

3.1 The KnockBack Cell

We define a **KnockBack** cell as follows:

KnockBack cell definition	
$q_0 = 0$	$\mathcal{B} = \{(f, (1/2, m))\}$, where:
$\lambda = 1/2, \sigma = 2, \omega = -2$	$f(x < 1/2) = 0$
$g(M > 0) = -(3/2)$	$f(1/2 \leq x < 1) = 1/2$
$g(M = 0) = 0$	$f(x \geq 1) = 1$
leader expression rule threshold: ≥ 2	

The **KnockBack** cell implements a natural symmetry breaking strategy. It is initialized with a low initial value of $q_0 = 0$ that is driven toward the equilibrium of $\sigma = 2$ at a gradient rate of $\lambda = 1/2$. As a cell's potential value passes through the range of $[1/2, 1)$, its single bioelectric event $(f, (1/2, m))$ fires with constant probability. If this event fires, the cell increases its potential by $1/2$ (e.g., by pumping in more ions), and emits the ligand m , which will bind with its neighbors in the topology. If at least one of the cell's neighbor emits the ligand m , then that cell will decrease its potential by $-(3/2)$ (e.g., by pumping out ions).

If a cell makes it to a potential value of 1 or greater, this event starts firing with probability 1. If a cell makes it to potential value of 2 or greater, it executes the *leader expression event*, which makes it a leader, and makes each neighbor below the threshold into non-leaders.

Two neighbors cannot both become leaders because any cell that becomes a leader in some round $r + 1$, must have spent round r at a potential value where it fires its bioelectric event with probability 1. If two neighbors fire this event in r , however, they both have a net decrease in their potential, preventing them from becoming leaders in $r + 1$. The time required for a leader to emerge is more complicated to derive, especially in the multihop context. The intuition behind these analyses, however, is that when multiple nearby cells simultaneously have potential values in the *competition range* of $[1/2, 1)$, it is likely that some will fire their event and some will not, aggregating inequality in their competition status until only a single leader remains.

3.2 Single Hop Leader Election

Consider a single hop (i.e., fully-connected) network consisting of $n > 0$ copies of the **KnockBack** cell defined in Section 3.1. We study the ability of this system to solve the leader election problem, which requires the system to converge to a state in which one cell is a leader and all other cells are non-leaders. We prove that the system never elects more than one leader, and that for any error probability $\epsilon > 0$, with probability at least $1 - \epsilon$ it elects a leader in $O(\log(n/\epsilon))$ rounds. As we detail in Section 1, this round complexity is comparable to the best-known solutions in more powerful computational models. Formally:

► **Theorem 1.** *Fix some error bound $\epsilon > 0$ and network of $n \geq 1$ **KnockBack** cells. With probability at least $1 - \epsilon$, a leader is elected within $O(\log(n/\epsilon))$ rounds. There is never more than 1 leader elected.*

The full proof, deferred to the full version of this paper (found on arXiv), tackles the liveness and safety properties separately. The safety property follows directly from the argument summarized above about the impossibility of two cells making it through the *gateway* potential where both would fire events and knock each other back out of immediate contention for leadership. The liveness argument proves that the set of contenders probabilistically bifurcates over time into two set A and B , where once in B a cell is no longer ever again in contention. We now provide a brief summary of the analysis.

Preliminaries

To understand the leader election process, we must first understand how the potential of a cell evolves. In each round, a cell c changes potential for three reasons: it sends a ligand, it receives a ligand, and the positive gradient, as summarized in this table:

	send	no send
receive	$-1/2$	-1
no receive	1	$1/2$

Safety

We now prove that at most one cell becomes leader.

► **Lemma 2.** *A single hop network comprised of **KnockBack** cells never elects more than one leader.*

Proof. Assume for contradiction that two different cells c and c' both become a leader during the same round $r > 1$.

Since c and c' first reached potential ≥ 2 in round r , the largest possible increase in potential is 1, and the smallest possible increase in potential is $1/2$, it follows that both must have started round $r - 1$ with a potential in $\{1, 3/2\}$.

Therefore, both c and c' sent ligands in round $r - 1$, and hence both c and c' decreased their potential by $1/2$ during round $r - 1$, starting round r with a potential in $\{1/2, 1\}$, contradicting the assumption that both cells are elected leader in r . ◀

Time Complexity

We now show that it does not take too long to elect a leader with reasonable probability. We first identify a set of contenders. Let $p(r)$ be the maximum potential of any cell in round r , and let $A(r)$ be the cells with potential $p(r)$; these are the contenders. Let $B(r)$ be all the other cells with potential $< p(r)$, i.e., the non-contenders. We can show, by a case analysis, that once a cell is no longer contending, it will never contend again:

► **Lemma 3.** *If cell c is in $B(r)$ in some round r , then cell c is in $B(r')$ for all $r' \geq r$.*

We say that a round is a *competition round* if there is at least one cell with potential at least $1/2$, and no cell with potential at least 1. In a contention round, there are at least some cells that send ligands with probability $1/2$, and no cell that sends ligands with probability 1. We can show, again by a case analysis, that competition rounds occur frequently:

► **Lemma 4.** *Fix some round $r \geq 1$. If r is a competition round then either: $r + 2$ is a competition round or a leader is elected by $r + 2$.*

Since (by definition) round 2 is a competition round, in fact, every even round will be a competition round. An important property of competition rounds is that with constant probability they reduce the number of cells in A by a constant fraction due to the case in which some cells send a ligand and some do not.

► **Lemma 5.** *If r is a competition round and $A(r)$ contains at least 2 cells, then with probability at least $1/12$, the set $A(r + 1) \leq (3/4)A(r)$.*

We can now conclude the proof that there is eventually one leader. We know that all the even rounds are competition rounds, and in each even round we reduce the competitor set $A(r)$ by a constant fraction with constant probability, as long as there are at least two competitors. The set $A(r)$ never becomes empty (as there is always some cell with the maximum potential), and never increases in size. Hence by a Chernoff Bound, with probability $1 - \epsilon$, within $O(\log(n/\epsilon))$ rounds there have been at least $\log n$ rounds in which $A(r)$ has been successfully reduced by a constant fraction, implying that at this point, the set $A(r)$ contains only one cell. The last remaining competitor becomes leader soon after that occurs.

3.3 Maximal Independent Sets

We now study the behavior of the **KnockBack** cell when executed in a multihop network topology that satisfies the natural *unit ball graph* property (see [23]). We show, perhaps surprisingly, that this simple cell efficiently solves the *maximal independent set* (MIS) problem in this context – providing what is arguably one of the simplest and most biologically-plausible explanations for how interacting cells might generate these useful patterns. Details and proofs can be found in the full version of this paper (posted on arXiv).

Solving the MIS problem requires that the system satisfy the following two properties: (1) *maximality*, every cell is a leader or neighbors a leader; and (2) *independence*, no two neighbors are leaders. We prove that the leaders elected by **KnockBack** in a multihop network always satisfy property 2, and that with high probability in the network size n , property 1 is satisfied in $O(\text{polylog}(\Delta) \log n)$ rounds, where Δ is the maximum degree in the network topology (and in many biological contexts, likely a small constant). We then show that the algorithm still efficiently *stabilizes* to an MIS even if we start cells at arbitrary potential values, an important property for noisy biological contexts.

As we elaborate in Section 1, the simplicity, efficiency, and stabilizing nature of generating MIS's with **KnockBack** leads us to hypothesize that bioelectrics might play a role in the observed generation of MIS patterns in the epithelial cells of flies [4]. The round complexity of our solutions, though not theoretically optimal, is comparable to existing solutions in more powerful computation models. Formally:

► **Theorem 6.** *Consider a network of $n \geq 1$ **KnockBack** cells connected in a unit ball graph G with constant doubling dimension and maximum degree Δ . With probability at least $1 - 1/n$, all cells terminate within $O(\text{polylog}(\Delta) \log(n))$ rounds, with the set of resulting leaders defining an MIS on G .*

Safety

First, we observe that if a cell reaches potential 1.5, then forever thereafter it continues to have high potential, while all of its neighbors remain with negative potential. This immediately implies that two neighbors cannot both be in the MIS. The argument here is nearly identical to Lemma 2.

► **Lemma 7.** *Let c and c' be two neighboring cells. It is never the case c and c' both have potential > 1.5 .*

Time Complexity

The more interesting task is proving that eventually, every cell or one of its neighbors will enter the MIS, and that this will happen quickly.

A cell is said to be in the MIS if it has potential at least 2. We analyze the behavior of *active* cells, i.e., those that are not in the MIS and that do not have any neighbors in the MIS.

We focus on cells whose potential is a local maximum, i.e., where every neighbor of c has potential no greater than that of c . If a cell is a local maximum, it may still have neighbors of equal potential – these are its competitors for entering the MIS. In fact, if a cell c is a local maximum and, and if cell c has approximately d competitors with equal potential, then it has (approximately) probability $1/d$ of entering the MIS within $O(\log \Delta)$ rounds.

We will want to identify cells that are likely going to enter the MIS quickly, or have a neighbor that is likely to enter the MIS quickly. We define a *quick-entry* cell as follows:

- Cell c is active.
- Cell c is a local maximum.
- Every neighboring competitor of c (with equal potential to c) is also a local maximum.
- If cell c has d neighboring competitors, then each of the neighboring competitors has at most $2d$ neighboring competitors of its own.

We will show that if c is a quick-entry cell, then either it or one of its neighbors will enter the MIS quickly, since each of these $d + 1$ cells has (approximately) probability $\geq 1/2d$ of entering the MIS (sidestepping issues of independence, which is the key challenge in proving this lemma).

► **Lemma 8.** *Consider the subgraph consisting only of active cells. Let c be a quick-entry cell. Then with probability at least $1/16$, either c or a neighbor of c enters the MIS within $O(\log \Delta)$ rounds.*

Proof (Sketch). Let S be the set consisting of c and its neighbors with the same potential. Let $s = |S|$. Notice every cell in S has at most $2s$ neighboring competitors, and recall that every cell in S is a local maximum.

In every round, we update S as follows: if $c' \in S$ is a cell in S , and if the current round is a competition round for c' in which c' does not send a ligand, then we remove c' from S .

S is the set of cells that remain candidates for entering the MIS, and every cell in S remains a local maximum. All the cells in S will maintain the same potential. Competition rounds are those in which cells in S have potential $1/2$. Cells in S continue entering competition rounds every other round until either S is empty or some cell in S enters the MIS.

A cell in S is a winner if, over $\log(4s)$ competition rounds: (i) it sends in all the competition rounds, and (ii) every one of its neighbors with the same potential, but *not* in S , has at least one competition round in which it does not send. Since each cell has at most $2s$ such neighbors, we can show that the probability that a cell in S wins is at least $1/(8s)$.

We can then analyze the event $W(c')$ that: (i) cell c' is a winner, and (ii) no other cell in S sends in all the competition rounds. These events are disjoint, and the probability of a cell in S sending in all the competition rounds is independent of the behavior of other cells in S . So we can show that for each cell c' in S , this event $W(c')$ occurs with probability at least $1/(16s)$.

This implies that with probability $\geq 1/16$, by the end of the competition rounds, there is exactly one cell c' in S that is a winner, and goes on to enter the MIS in $O(1)$ rounds. ◀

Next, we show that there is always a quick-entry cell no more than $O(\log \Delta)$ hops away:

► **Lemma 9.** *Consider the subgraph consisting only of active cells. For every cell c' active in round r , there exists a quick-entry cell c within distance $O(\log \Delta)$.*

Proof (Sketch). The proof of this is constructive, beginning at cell c and moving through the graph until we find a suitable cell not too far from c .

Beginning at c , we repeatedly move to any active cell within distance $(\log(\Delta) + 2)$ that has larger potential. Since potential ranges from -3 to 2 by multiples of $1/2$, within 10 steps this process stops at some c' . All the cells with the same potential as c' within distance $\log(\Delta) + 2$ of c' are local maxima.

Next, we repeat the following: If c' has d neighbors that are competitors (i.e., have the same potential), and if any neighbor of c' that is a competitor has more than $2d$ neighbors that are competitors, then we move to that neighbor. Since the number of neighboring competitors doubles at each step, this terminates within $\log \Delta$ rounds.

The resulting cell is a quick-entry cell, and within distance $O(\log(\Delta))$ of the initial cell c . ◀

Putting together the previous two lemmas, we conclude:

► **Lemma 10.** *Given any cell c active in round r , with probability at least $1/16$ there is a cell within distance $O(\log \Delta)$ that enters the MIS within $O(\log \Delta)$ rounds.*

Finally, we leverage the assumption that the underlying graph topology $G = (V, E)$ is a UBG with constant doubling dimension. A graph $G = (V, E)$ is UBG [23] if it satisfies the following two constraints: (1) there exists an embedding of the nodes in V in a metric space such that there is an edge $\{u, v\}$ in E if and only if $\text{dist}(u, v) \leq 1$; and (2) the doubling dimension of the metric space, defined as the smallest ρ such that every ball can be covered by at most 2^ρ balls of half its radius, is constant. (In the real-world, where physical cells are embedded in a two or three-dimensional Euclidean space and neighboring cells can interact, the resulting topology is UBG.) UBG graphs provide the following standard property:

► **Lemma 11.** *For every independent set I and cell c , there are $O(k^\rho)$ cells in I within distance k of c .*

We can now prove Theorem 6 by arguing that for a cell c , it either enters the MIS or it has a quick-entry cell within distance $O(\log(\Delta))$ that enters the MIS with constant probability. Since there are a bounded number of cells within distance $O(\log(\Delta))$ that can legally enter the MIS (due to the UBG property), we can bound how long until cell c is no longer active.

Stabilization

Throughout the analysis above, we assumed for simplicity that all the cells began with potential precisely zero. However, it turns out that is not in fact necessary. Notably, if the potentials begin too low, e.g., < -3 , then eventually the potential climbs into the normal range (due to the gradient effect), unless a neighbor joins the MIS first and preempts it. Alternatively, if potentials begin too high and two neighboring nodes have potential > 1 , then they will continue to send in every round and hence eventually one or both will exit the MIS, with their potential dropping below 2. Once safety has been restored, i.e., no neighbors are in the MIS, then the system will stabilize as already described. Nowhere in the analysis did we depend on any special initial conditions or relations between the potentials. Thus we conclude:

► **Theorem 12.** *Consider a network of $n \geq 1$ **KnockBack** cells connected in a unit ball graph G with constant doubling dimension and maximum degree Δ . Assume that the cells begin with arbitrary potentials. Then eventually, with probability 1: no two neighboring cells are in the MIS, and every cell is either in the MIS or has a neighbor in the MIS.*

4 Input Type Computation

We now turn our attention to processing information, beginning with a problem studied in bio-inspired chemical reaction networks and population protocols: computation on input type counts. For these problems the *input* is the *a priori* unknown counts of the different cell types in the system. We look at two commonly studied problems: threshold and majority detection, establishing that these problems are tractable in the CBM, but require randomized solutions with non-zero error probabilities. Full details appear in the full version of the paper (posted on arXiv).

4.1 Threshold Detection

The threshold detection problem, which is parameterized with a threshold k , approximation factor τ , and error bound ϵ , and requires a correct answer if the number of sick cells is larger than $\tau \cdot k$, or less than k/τ (see the full version of the paper for the formal definition).

For the sake of completeness, in the full version of this paper we start by describing and analyzing a simple cell definition called **SmallThreshold**(k), that works when the binding bound (see Section 2) is large enough for cells to directly count up to k , trivializing the problem, even for $\epsilon = 0$ and $\tau = 1$. For larger k values, we consider the following more general probabilistic solution:

GeneralThreshold(k) cell definition	
$q_0 = 1$	$\mathcal{B} = \{(f, (2, m))\}$, where:
$\lambda = 1, \sigma = 0$	$f(x \geq 1) = 1/k$
$g(M \geq 1) = 2$	$f(x < 1) = 0$
$g(M < 1) = 0$	
event threshold: 2	

The **GeneralThreshold**(k) cell has cells fire a bioelectric event with probability $1/k$. If *any* cell fires, it moves itself past the event threshold, otherwise, the system falls back to a quiescent equilibrium. In the full version of the paper, we show a strict trade-off between the error bound and τ approximation:

► **Theorem 13.** *Fix any error bound $\epsilon, 0 < \epsilon < 1$ and threshold $k \geq 1$. Then the **GeneralThreshold**(k) cell definition solves the $(k, 8 \ln(1/\epsilon), \epsilon)$ -threshold detection problem in one round.*

Another possible improvement would be removing the non-zero error bound (i.e., achieving $\epsilon = 0$), or finding a deterministic solution. We prove such improvements are impossible (see the full version for more details):

► **Theorem 14.** *Fix a binding bound $b \geq 1$, threshold range $\tau \geq 1$, and round length $T \geq 1$. There does not exist a cell definition with binding bound b that solves the $(k, \tau, 0)$ -threshold detection problem in T rounds for every threshold $k \geq 1$. Fix $\epsilon, 0 \leq \epsilon < 1/2$. There does not exist a deterministic cell definition with binding bound b that solves the (k, τ, ϵ) -threshold detection problem in T rounds for every threshold $k \geq 1$.*

4.2 Majority Detection

Majority detection assumes two cell types: A and B . The goal is to determine which type is more numerous. As with threshold detection, and most existing studies of majority detection in other models (e.g., [7]), we look at approximate solutions that ensure a correct answer only if one count is sufficiently larger than the other. We tackle this challenge with the below cell definition which is parameterized with an upper bound N on the maximum network size and a constant error bound $\epsilon > 0$:

MajorityA($N, \alpha = \lceil 2 \ln(2/\epsilon) \rceil$) cell definition (for type A)	
$q_0 = 0$	$\mathcal{B} = \{(f, (\alpha \log N, m_A))\}$, where:
$\lambda = 1, \sigma = 3\alpha \log N$	$f(0 \leq x \leq \alpha \log N) = 2^{-(\log N - \lfloor \frac{x}{\alpha} \rfloor)}$
$g(M_B \geq 1) = -2\alpha \log N$	$f(x < 0) = 0$
$g(M_B = 0) = 0$	$f(x > \alpha \log N) = 1$
event threshold: $3\alpha \log N$	
$(M_B \text{ equals the sub-multiset including only ligands of type } m_B \text{ sent from type } B \text{ cells.})$	

This cell implements a common backoff style strategy, perhaps inspired from radio networks, where nodes fire with increasing probabilities. The first cell type to fire is assumed to be the majority type in the system. In the full version of this paper, we show a trade-off between ϵ and the required size gap between the cell type counts:

► **Theorem 15.** *Fix some constant error bound $\epsilon > 0$ and upper bound $N > 1$. Let $\alpha = \lceil 2 \ln(2/\epsilon) \rceil$. The MajorityA(N, α) and MajorityB(N, α) cell definitions, when executed in a system with n_A and n_B type A and type B cells, respectively, where $n_A > n_B \cdot (\alpha 4)/\epsilon$ and $N \geq n_A + n_B$, guarantees with probability at least $1 - \epsilon$: in the first $O(\log n)$ rounds, a type A expression event will occur before any type B event. (The symmetric claim also holds for $n_B > n_A \cdot (\alpha 4)/\epsilon$.)*

5 Turing Completeness

Finally, we consider another natural definition of information processing in which cells compute functions on an input encoded in the potential of a designated *input cell*. This isolates a core question: *What types of computations on cell states can be computed through simple bioelectric interactions?* In the full version of the paper (posted on arXiv), we prove a perhaps surprising answer: Essentially all feasible computations.² Formally:

► **Theorem 16.** *Fix an arbitrary deterministic TM M . There exists a finite collection of cells defined with respect to M , including a designated input cell, such that for every TM input w , if you set the input cell's initial potential value to a specified unary encoding of w , the cells will correctly simulate M on w .*

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² Turing completeness is relatively common in restricted state machine models, yet it did not seem *a priori* obvious whether the CBM would satisfy this property as *computation* in the CBM is restricted to simple bioelectric interactions.

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