

Signal transmission through excitable media by an oscillatory source

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(Received 14 June 2024; accepted 18 December 2024; published 3 March 2025)

Living organisms transmit signals through local interactions with their neighbors. However, the precise timing of signals is fundamentally challenged by the presence of numerous stochastic reactions within interacting cells. Here we develop a minimal model to investigate the strength of signal propagation in stochastic environments. We uncover a multimodal frequency dependency with a few local optima, which is robust in both one and two dimensions. Through mathematical analysis we explain the frequency dependency and uncover the interplay between stochasticity and external frequency in order to optimize the signaling strength of the system. Finally we investigate the possibilities of bidirectional reactions in the oscillating source, allowing us to define thermodynamic properties of the system and investigate the relationship between free-energy dissipation and precision of signaling, showing nontrivial frequency dependency in coupled cells.

DOI: [10.1103/PhysRevResearch.7.L012051](https://doi.org/10.1103/PhysRevResearch.7.L012051)

The transmission of signals in cell cultures or tissues is a key task for living organisms. In order to efficiently send signals, living organisms rely on precise timing between interacting cells. For a signal to be transmitted through a tissue of cells, a wave of signal should travel through an excitable medium [1].

Excitable systems possess common fundamental traits. They maintain a stable resting state, where signals that typically exceed a specific threshold initiates a reaction that is passed on to the neighboring environment. Following this rapid response, the system enters a refractory period before eventually regaining its full excitability [2].

A typical phenomenon arising from excitable media are traveling waves, that have been observed in chemical, physical, and biological activities. The best known example, operating on short time scales is the neural action potential, where an electrical signal travels along an axonal membrane [3]. In chemical reactions, traveling waves have been observed in numerous systems [4–7], more recently also in bacterial communities [8,9]. On a larger and slower scale, waves of infectious diseases travel through biological populations, where the recovery time is set by the time scale by which agents lose immunity [10,11].

In biology, a classical example of a traveling wave is vertebrate development, where the embryonic body axis segments into somites via a process known as somitogenesis [12,13]. Here, the timing of the traveling wave is crucial to

obtain correct segmentation of cells and thereby functioning development of the embryo [14]. However, the timing of the traveling wave is obtained between individually oscillatory cells, that form spatial couplings [15,16]. In this Letter we consider the situation where living organisms transmit a signal through tissue consisting of nonoscillatory cells, with a specific refractory period. As a model system for this we consider the cellular signaling in, for instance, wound healing that require coordination of cells from multiple tissues [17,18] and therefore coordination of cellular response within and between tissues is fundamental for a well-functioning process [19]. Of specific importance in the process is the transcription factor NF- κ B [20], which has been shown to oscillate in the nuclear concentration in fibroblast cells following stimulation of the ligand Tumor Necrosis Factor (TNF) [21–23]. How cells can optimize the signaling efficiencies through tissue remains an unresolved question and at this stage the role of intracellular dynamics in specific cells (fibroblasts) and how that affects a larger population (tissue), has not been studied.

In this Letter we show that signal transmission for stochastic systems is optimized through an external, periodic regulator. Inspired by the oscillations in NF- κ B, we reveal that there exist specific frequencies that enhance transmission efficiency, and derive one global optimum. Our exploration encompasses the integration of thermodynamic principles and the assessment of alternative performance metrics, with a particular focus on the oscillating source's capacity to temporally coordinate events within the cellular environment.

Model. To investigate the properties of signal transmission in interconnected cells, we constructed a simple model inspired by the architecture of a population of N cells on a line. The model is schematically shown in Fig. 1. We assume that each cell can be in three states with distinct properties:

(i) **Receptive:** The cell can receive a signal from its neighboring cell.

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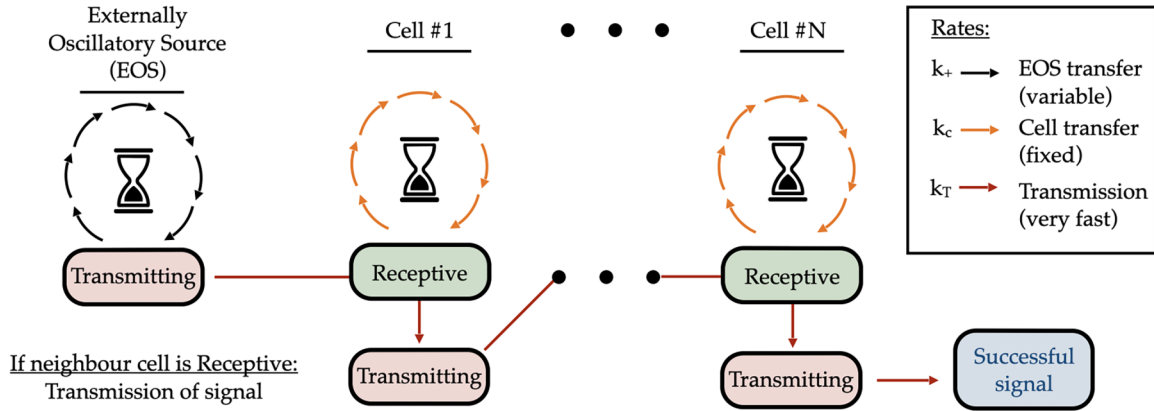


FIG. 1. Schematic visualization of the one-dimensional, unidirectional system. Arrows indicate the specific rates defining the behavior of the system.

(ii) Transmitting: The cell can propagate the signal to its neighbor if the neighbor is in the receptive state.

(iii) Inactive: The cell can neither receive a signal from the environment nor transmit signal to neighbors.

A core aspect of the model involves cells processing multiple chemical reactions to achieve the receptive state. Each of these reactions is assigned a rate k_C , resulting in a characteristic time $\nu = \frac{L_\nu}{k_C}$, where L_ν is the number of transitions a cell must undergo from the transmitting state to the receptive state. Once a cell in the receptive state receives a signal, it propagates it with rate k_T , where $k_T \gg k_C$ unless stated otherwise. To initiate the signal, a periodically stimulated cell is introduced in the first column (Fig. 1, left), acting as an external oscillating source (EOS). This cell undergoes transitions between transmitting and inactive states, governed by rates k_+ . This gives the EOS a characteristic time $\mu = L_\mu/k_+$, with L_μ denoting the number of transitions the EOS must undergo to go from the transmitting state and back again. A successful signal is defined as a signal transmission to the N th cell. To numerically study this system, we employ a Gillespie-style algorithm [24]. Unless specified otherwise, we use $L_\mu = L_\nu = 100$ and $k_C = 1$ as standard parameters. As a natural consequence of the exponential distribution, the standard deviation of the time it takes to complete each transition for the cells is $\frac{1}{k_C}$, while the standard deviation of the EOS transitions is $\frac{1}{k_+}$. We refer to these deviations from the means as the noise of the system.

Results. Based on the model presented above, we simulated the system and measured the number of successful signals. For $N = 1$ [Fig. 2(a), green line], we observed a nonmonotonic but simple dependence on k_+ , peaking at high frequencies due to prompt signal transmission by the EOS. Conversely, with $N = 100$, we found a nontrivial frequency dependence with multiple local optima [Fig. 2(a), blue solid line]. In both the $N = 1$ cell system and the $N = 100$ cell system, the locations of the optima differ from the optima in the deterministic limit [Fig. 2(a), black vertical dotted lines] of the system, highlighting the significance of noise.

Stochasticity introduces the possibility of *failed signals* where an initiated signal does not complete its course. We measure how far a failed signal reaches on average [Fig. 2(b), red line] and what the probability of a failed signal

is [Fig. 2(b), blue line] as a function of k_+ . Both display clear frequency dependence, with a tendency that failed signals are more probable and less sensitive to small variations of the frequency in the high-frequency regime. In this regime, the first cell waits only a short time for the EOS to transmit a signal, so it is likely that a signal will be initiated before all cells are receptive. In contrast, premature signal initiation is less likely in low-frequency regimes, but if it occurs, it will likely be due to unusually delayed receptivity in a random cell that hinders signal completion, meaning that the failed signal will often have penetrated further. To test the rigidity of our findings, we measured the extent of the failed signal and the probability for a signal to fail for many different values of both k_+ and k_C . We observe that both measured quantities strictly depend on the ratio k_+/k_C . The findings here also highlight that it is not beneficial if the ratio k_+/k_C takes on an integer value, as that causes failed signals to be quite likely due to noise. But when the number of completed signals is plotted as a function of k_+/k_C , peaks appear at the same values across all values of k_C (see Appendix, Fig. 5). In a one-dimensional (1D) system with 100 cells, in the limit of infinitely fast transmission rates, it is therefore always the case that the ideal value of k_+ for maximum signal propagation is approximately $1.4 \times k_C$.

The observations underscore the critical role of noise in the system, so to capture this mathematically, we model the time for the EOS to transition between transmitting states $i \in \mathbb{N}$ times using the normal distribution $X_i \sim \mathcal{N}(\mu_i, \sigma_i)$ where $\mu_i = i\mu$ and $\sigma_i = \sqrt{i} \frac{\sqrt{L_\mu}}{k_+}$ so that $\sigma = \frac{\sqrt{L_\mu}}{k_+}$. Similarly, each cell's time spent between the transmitting and receptive states is $Y \sim \mathcal{N}(\nu, \epsilon)$, where $\epsilon = \frac{\sqrt{L_\nu}}{k_C}$. These approximations are valid when L_ν and L_μ are large. Using the normal distributions, we introduce the probability $P(X_i > Y)$ that the i th realization of X is greater than a single realization of Y . As such, in an $N = 1$ system, the probability that the signal occurs at time $\tau_1 = \mu_i$, must be weighed by the probability that an earlier realization of X did not already initiate a signal, giving us an average time of signal initiation

$$\langle \tau_1 \rangle = \mu \sum_i \left[iP(X_i > Y) \prod_{j=1}^{i-1} [1 - P(X_j > Y)] \right]. \quad (1.1)$$

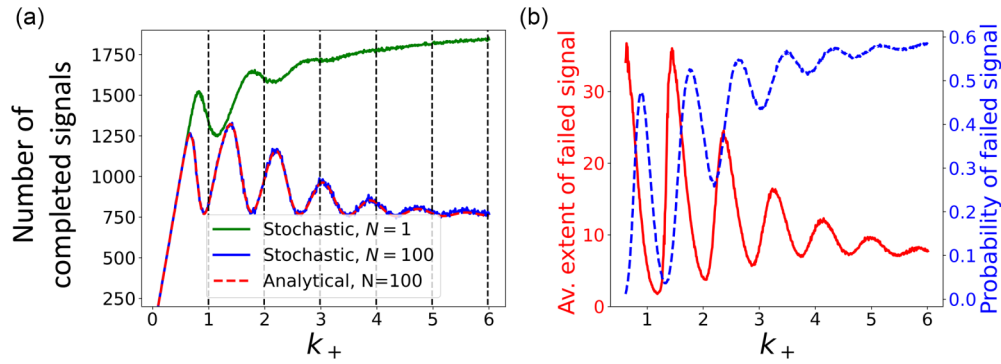


FIG. 2. One-dimensional system. (a) Number of signals registered in the first cell and the 100th cell after simulation with standard parameters as a function of k_+ . The red dotted line shows the result of our mathematical model of Eq. (1.4), specifically $\langle \tau_{100} \rangle / T$. Black dotted lines indicate the optimal frequencies in the deterministic system. (b) Average extent of a failed signal (red) and probability of having a signal fail (blue), simulated with standard parameters in an $N = 100$ system. The average extent refers to the number of cells the signal reaches before encountering a nonreceptive cell. Here, data is only included if more than 20 failed signals were observed during the simulation.

The distribution of τ_1 follows the probability density function (PDF)

$$p(\tau_1) = AP(\tau_1 > Y) \sum_{i=1} \left[f_{X_i}^*(\tau_1) \prod_{j=1}^{i-1} P(X_j < Y) \right], \quad (1.2)$$

where A is a normalization constant and $f_{X_i}^*(\tau_1)$ is a modified PDF of X_i (see Appendix, Fig. 6). Equation (1.1) reflects the results seen in Fig. 2(a) (green line). We now include more cells, incorporating failed signals in our description. For an $N = 2$ system, the time it takes to send a successful signal is on average

$$\begin{aligned} \langle \tau_2 \rangle &= \int_{-\infty}^{\infty} p(\tau_1) P(\tau_1 > Y) \tau_1 d\tau_1 \\ &+ \int_{-\infty}^{\infty} p(\tau_1) (1 - P(\tau_1 > Y)) (\tau_1 + \langle \tau_1 \rangle) d\tau_1, \end{aligned} \quad (1.3)$$

where the first term represents the time it takes to send a signal that successfully reaches the first and second cell, and the second term represents the time it takes to reach the second cell, should the first signal fail. This additional time will be the sum of the time to transmit the signal that fails and the time to transmit a signal that reaches the first cell. With this information, we can deduce how long it would take to transmit to the third cell in an $N = 3$ system, and extending to N cells with an iterative process, giving us

$$\begin{aligned} \langle \tau_N \rangle &= \langle \tau_1 \rangle + \sum_{n=1}^{N-1} \left[\langle \tau_n \rangle \int_{-\infty}^{\infty} p(\tau_1) (1 - P(\tau_1 > Y)) \right. \\ &\quad \left. \times P(\tau_1 > Y)^{n-1} d\tau_1 \right]. \end{aligned} \quad (1.4)$$

Based on this calculation, we can estimate the resulting number of successful signals, $S = T / \langle \tau_N \rangle$ where T is the duration of the simulation. By comparing this to the numerical simulations we find a good agreement [Fig. 2(a), red dotted line]. By this mathematical advancement, we now have a full understanding of the signal transmission for a 1D line of cells. To generalize the system we construct a two-dimensional (2D)

model, arranging N cells in concentric rings, and connecting the cells using Delaunay triangulation [Fig. 3(a)]. In this model we define a successful signal as an initiated signal, that reaches all cells in the population. Two different neighboring schemes were tested: (i) signal transmission to all connected cells, and (ii) signal transmission directed radially outward. Qualitatively, we only observe transmission in narrow fingers with spatial division for (ii) [Fig. 3(a)].

As in the 1D system, we compute the number of successful signals and observe larger amplitudes as compared to the 1D system indicating a higher frequency sensitivity [Fig. 3(b)]. This can be understood since a failed signal is more likely to be transmitted to a significant portion of the cells due to the larger connectivity in the 2D system. This increased neighbor connectivity also boosts resilience to lower transmission rates (k_T) compared to the 1D system. Fixing the optimal value of k_+ , we calculate the number of successful signals as a function of the transmission rate k_T . We find that the 2D configuration is significantly more robust to low rates of k_T , as it reaches the optimal signal strength at values two orders of magnitude lower compared to the 1D system [Fig. 3(c)]. The implications of this is that while a 1D system would require radically different time scales for signal transmission and relaxation time in order to secure efficient propagation across the system, the two-dimensional system allows for efficient propagation if the transmission takes place on transmission of seconds while the relaxation back to the receptive state takes place on the time scale of minutes. For a hypothetical three-dimensional (3D) system, the implication would then be even less dependence on k_T , but a still greater discrepancy between optimal and suboptimal frequencies. The lower dependence on k_T means that there are even less strict requirements for the difference in time scales between relaxation and transmission.

In the 1D system, we also tested the influence of changing only the transmission rate between the EOS and the very first cell, referred to as $k_T^{(1)}$. Together, the results show that high values of k_+ that normally give suboptimal performance benefit from lower $k_T^{(1)}$ (see Appendix, Fig. 7). The lower transmission rate means that fewer signals are initiated overall, which is beneficial in the high k_+ regime. This is because many signals in this regime are initiated before all cells are receptive. If such a signal is not initiated due to low transmission rate, but

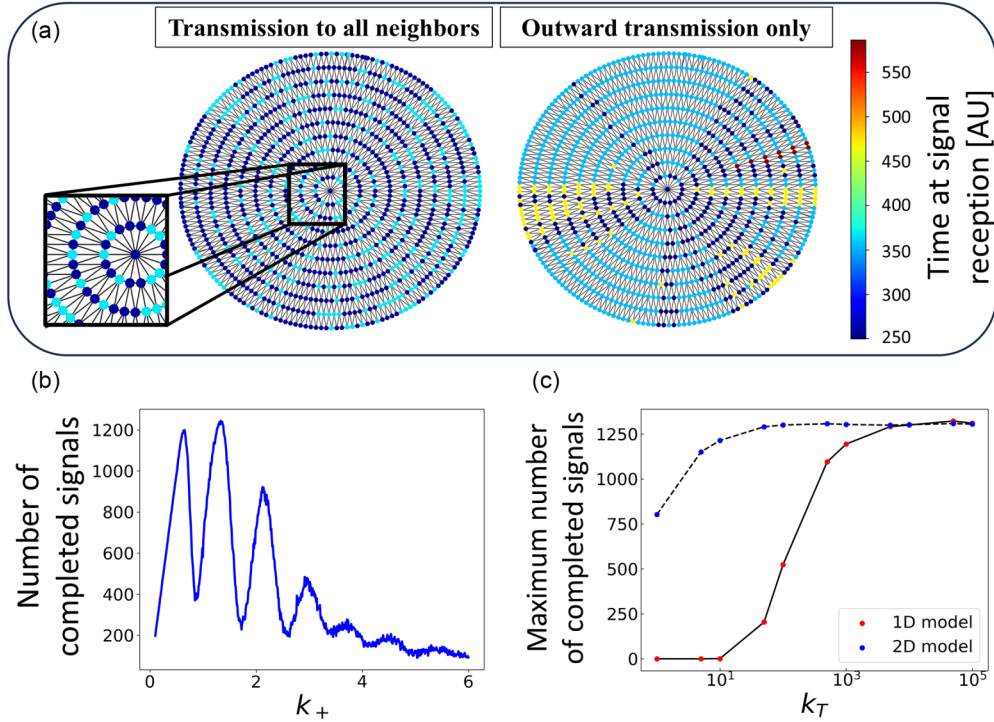


FIG. 3. Simulations in two dimensions. (a) Example of how a signal might propagate on a two-dimensional system with cells connected through Delaunay triangulation, with the colors indicating the point in time at which a cell received a signal. Simulated with $k_T = 100$. Left: Simulation performed with coupling scheme where signal transmission is possible to all receptive neighbors. Showcased here is also a zoomed-in view, showing the connections between cells facilitated by Delaunay triangulation. Neighboring cells belonging to the first same concentric ring are also connected. Right: Simulation performed with coupling scheme where cells only transmit outward. (b) Number of successful signals as a function of k_+ in an $N = 400$ 2D system with 6 concentric rings, where cells can transmit to all neighbors. (c) The highest number of successful signals registered across all values of k_+ as a function of signal transmission rate k_T , comparing the one-dimensional system with 100 cells to a 2D concentric ring model with 100 cells in 3 rings.

only initiated the next time that the EOS is transmitting, there is a greater chance that all cells are receptive. Since the EOS is relatively fast in this regime, the cells will not wait long in the receptive state regardless. On the other hand, at optimal values around the first and second peak in the lower k_+ regime, fewer initiated signals mean that cells will end up waiting longer in the receptive state, causing fewer signals to be completed. Since failed signals are already rare here, the lower $k_T^{(1)}$ does not have a noticeable positive effect on performance.

So far, we have only considered the number of signals transmitted, but in many systems the precision of timing could also be an important determinant. High precision could be of interest if the process we are investigating needed to be synchronized with other cellular processes. Since the desired system should be able to both propagate many signals and do it with high temporal precision, we introduce the signal-to-noise ratio (SNR) defined as $SNR = \frac{S(N)}{\rho}$, where ρ is the standard deviation of the periods measured in the cells. Notice that ρ is a distinct quantity from ϵ , as ϵ is the standard deviation of the time spent in the inactive states, and only a function of cell parameters, while ρ stems from an interplay between cell parameters and EOS parameters. It has previously been shown that there exist clear relationships between the precision and free-energy dissipation of a stochastic process [25]. To include free-energy dissipation in our system, we now define the EOS as a dissipative structure constituting a series of bidirectional transitions between inactive states

and a single unidirectional transition between the transmitting state and the first inactive state. The transition rate in the direction of the transmitting state is k_+ , and the transition rate in the opposite direction is k_- . In the entropy production, we ignore the unique contribution of the single unidirectional transition, which generally has a different contribution [26], as it constitutes only a single transition among many. With constant reservoir temperature $T = 1$ and Boltzmann constant $k_b = 1$, the entropy production and free-energy dissipation are equivalent and can be written

$$s = \mathcal{A}(k_+ - k_-), \quad (1.5)$$

where $\mathcal{A} = \ln \frac{k_+}{k_-}$ is the thermodynamic force driving the reaction and $(k_+ - k_-)$ is the thermodynamic flux. The introduction of k_- changes the dynamics so the normal distribution approximations from above do not apply anymore, but as long as k_- is low compared to most k_+ , a similar pattern to that of Fig. 2(a) still appears here. In Fig. 4, we show the SNR as a function of the entropy production rate, and see clear frequency/energy investment dependency, with narrow peaks since the poorly performing frequencies/entropy production levels with high risk of failed signals both affect the number of signals that reach the final cell but also strongly affects ρ . This result is rather robust to different values of k_- . This framework shows that the inherent frequency dependency of the system also allows for a dependence on the free-energy investment in

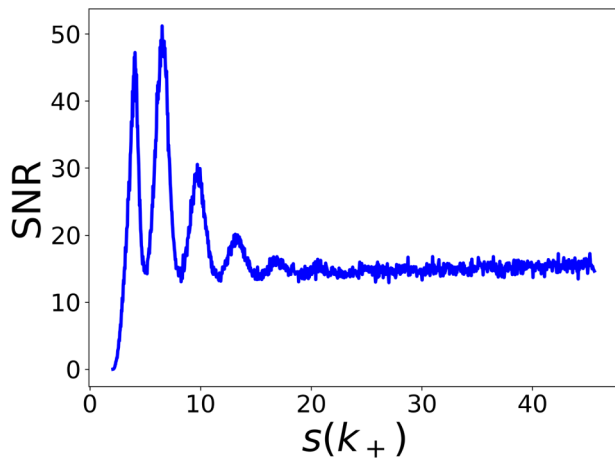


FIG. 4. Signal-to-noise ratio as a function of the entropy production rate with $k_- = 0.1$ in an $N = 100$ system.

a given process. The exact dependency that we see once again stems from the stochasticity introduced by the inclusion of multiple cells which substantially compromises the ability for energetically expensive and fast EOSs to perform well. The observations in our minimal model show how the interplay between characteristic relaxation times and the presence of noise in interconnected cells make the system benefit from an external source with a specific frequency, in the sense that the transmission of signals across cells is more efficient. We see that the frequency dependency is specifically one that emerges in systems of many coupled cells. In our analytical main result, Eq. (1.4), it was found that the ideal external frequency was one that was relatively fast, but still secured that the distribution of signal initiation times were mostly unimodal, so the risk of the stochasticity of the cells influencing how far into the row of cells the signal reaches is minimal. The resulting frequency dependency is rather robust, only breaking down when signal transmission is too slow. By incorporating

energetic relationships, we gained another perspective on the system, and saw that the presence of noise allows for less precise EOSs closer to equilibrium to outperform more energetically costly EOSs when measuring SNR. Since noise is an unavoidable feature of biological systems, this could perhaps incentivize the evolution of frequency-dependent processes.

Acknowledgments. M.L. acknowledges funding from the Carlsberg Foundation, Grant CF22-0494. M.H.J. acknowledges funding from The Novo Nordisk Foundation, Grants NNF20OC0064978 and NNF24OC0089788. M.S.H. acknowledges funding from The Novo Nordisk Foundation, Grant NFF23OC0085907.

Appendix: Probability density function of signal initiation time. In the derivation of Eq. (1.4) in the main text, we needed the probability density function for the time of signal initiation, which is Eq. (1.2) in the main text. Equation (1.2) is repeated here:

$$p(\tau_1) = AP(\tau_1 > Y) \sum_{i=1} \left[f_{X_i}^*(\tau_1) \prod_{j=1}^{i-1} P(X_j < Y) \right], \quad (\text{A1})$$

where Y is the stochastic variable with distribution $Y \sim \mathcal{N}(v, \epsilon)$ and X is the stochastic variable $X_i \sim \mathcal{N}(\mu_i, \sigma)$ where $\mu_i = i\mu$. The probability density functions (cumulative distribution functions) of these random variables are $f_Y(t)$ [$F_Y(t)$] and $f_{X_i}(t)$ [$F_{X_i}(t)$]. The probability that a cell is receptive by the time τ_1 is simply $P(\tau_1 > Y) = F_Y(\tau_1)$.

The product $\prod_{j=1}^{i-1} P(X_j < Y)$ represents the probability that an earlier realization of X did not already initiate a signal. As an integral, this can be written $\prod_{j=1}^{i-1} (1 - \int_0^\infty f_{Z_j}(t) dt)$, where $f_{Z_j}(t)$ is the probability density function of the random variable $Z_i \sim \mathcal{N}(\mu_i - v, \sqrt{i\sigma^2 + \epsilon^2})$. The integral can be evaluated analytically.

$f_{X_i}^*(\tau_1)$ is a modified probability density function of X_i which takes on a slightly more complicated form. Consider that the EOS completes a single cycle. In that case, we can with high confidence say that the mean value of the cycle

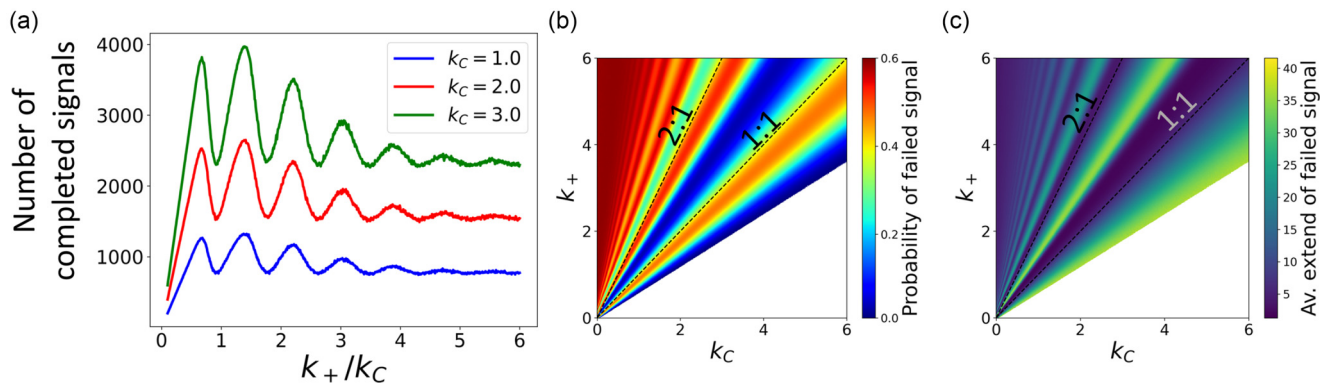


FIG. 5. The influence of k_C and the significance of the ratio k_+/k_C in a 1D system with $N = 100$. (a) Number of completed signals as a function of the ratio k_+/k_C for three different values of k_C . The result shows that even though higher k_C naturally allows for more signals if k_+ , the pattern, including the location of peaks is a function of the ratio k_+/k_C . (b) Heatmap showing the probability of having a signal fail as a function of k_+ and k_C . The white region is the region of parameter space where the probability of a failed signal is below 0.01, since the cells are virtually guaranteed to be ready before the EOS is transmitting. As described in the main text, this region is quite ineffective in signal propagation. The black dotted lines indicate where the ratios k_+/k_C are 1 and 2, respectively. We see that the probability of having a signal is constant for varying k_+ and k_C , if the ratio is conserved. (c) Same as (b), but showing the average extent of recorded failed signals. Similarly to (b), we see that the crucial behavior of the system depends on the ratio k_+/k_C .

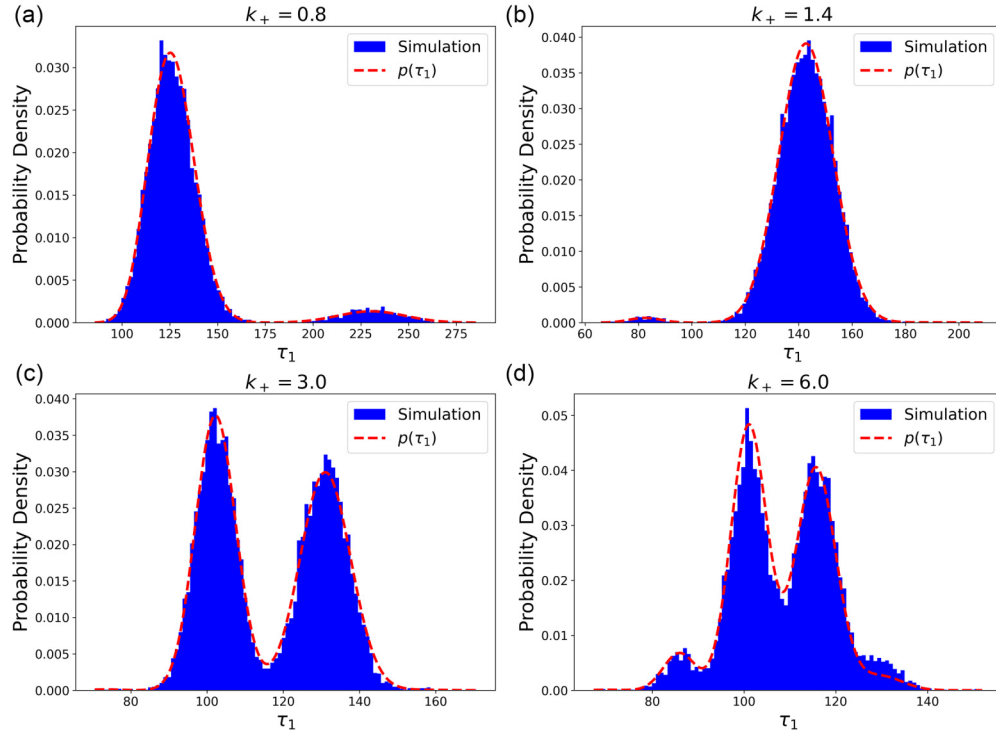


FIG. 6. Equation (A1) compared to simulations of signal initiation times for four different values of k_+ showing four distinct situations. (a) Since the cell has a characteristic time of $\nu = 100$, we see that $k_+ = 0.8$ allows for relatively fast signal initiation, with a risk of not transmitting a signal after a single EOS cycle. In that case, the signal will be transmitted much later, leading to the bimodality of the distribution. Since the cell in many cases waits only a short time for the signal from the EOS, $k_+ = 0.8$ does come with a substantial risk of failed signals, if the system contains many cells. (b) EOS with $k_+ = 1.4$ is very well performing in general. We see that the distribution is quite unimodal. There is a slight risk of very early signal transmission, which will very likely result in a failed signal. (c) $k_+ = 3.0$ gives a bimodal distribution with one peak close to $\tau_1 = 100$, the characteristic time of the cell. This is likely to result in a failed signal. (d) $k_+ = 6.0$ results in a highly multimodal distribution with four observable peaks. Some of these peaks are found at relatively low values of k_+ , meaning that failed signals are quite likely to occur.

is $\mu_1 = \frac{100}{k_+}$. In general, we also know that the second cycle will be finished at $\mu_2 = \mu_1 + \mu_1$ on average, but if we know that a completion of the first cycle did not result in signal

transmission, the mean value of the completion of the second cycle must be updated with this information, meaning that the *modified mean* of the distribution is $\mu_2^* = \mu_1 + \langle X_1 | X_1 < Y \rangle$

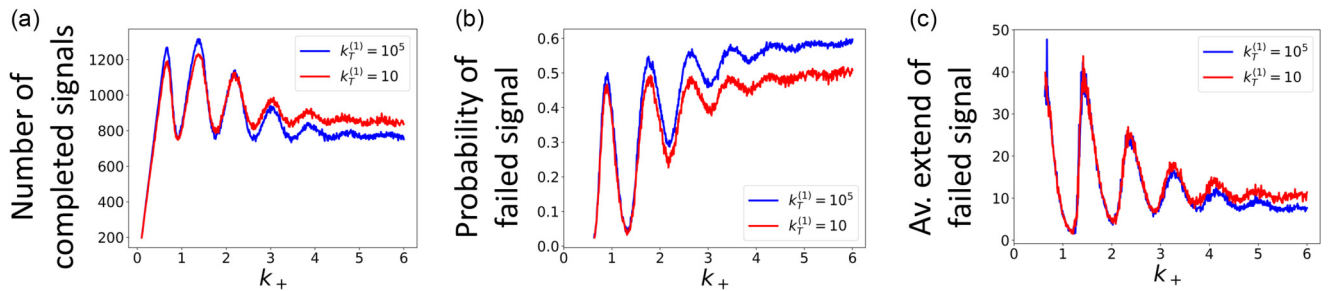


FIG. 7. The influence of $k_T^{(1)}$, the transmission rate between the external oscillating source and the first cell, as explained in the main text. Simulations were conducted in the 1D system with $N = 100$. To see noticeable differences between simulations, the difference in $k_T^{(1)}$ must be very high. Here, we show results for $k_T^{(1)} = 10^5$ and $k_T^{(1)} = 10$. Together, the results show that high values of k_+ that normally give suboptimal performance benefit from lower $k_T^{(1)}$. (a) Number of completed signals as a function of k_+ , shown for the two tested values of $k_T^{(1)}$. Results show that slower EOSs, specifically in the regions around the peaks, benefit from high $k_T^{(1)}$ while faster EOSs benefit from low $k_T^{(1)}$. (b) Probability of a signal failing as a function of k_+ , shown for the two tested values of $k_T^{(1)}$. Data has only been included if more than 20 failed signals were observed. This provides an intuitive explanation for the results shown in (a). At the optimal values of k_+ in the low k_+ regime, the probability of seeing failed signals is largely unaffected, while at suboptimal values of k_+ in the low k_+ regime and at all values in the high k_+ regime, we see greater risk of having signals fail when $k_T^{(1)}$ is high. (c) Average extent of failed signals as a function of k_+ , shown for the two tested values of $k_T^{(1)}$, showing slight differences, with failing signals at low $k_T^{(1)}$ penetrating slightly deeper into the cells.

where $\langle X_1 | X_1 < Y \rangle$ is the mean value of the stochastic variable X_1 given that it is lower than Y . This carries over to future cycles giving us a modified mean value for the i th realization of the EOS,

$$\mu_i^* = \mu_1 + \langle X_{i-1} | X_{i-1} < Y \rangle. \quad (\text{A2})$$

As an integral, we can write this expectation value

$$\begin{aligned} \langle X_{i-1} | X_{i-1} < Y \rangle &= \int_{-\infty}^{\infty} t(1 - B \cdot F_Y(t)) f_{X_{i-1}}(t) dt \\ &= \int_{-\infty}^{\infty} t f_{X_{i-1}}(t) dt - B \int_{-\infty}^{\infty} t F_Y(t) f_{X_{i-1}}(t) dt, \end{aligned} \quad (\text{A3})$$

where $B = \frac{1}{1 - F_{Z_{i-1}}(0)}$ is a normalization constant which ensures that $B \times F_Y(t) f_{X_{i-1}}(t)$ is a normalized probability density function. The first term has the well known solution $\int_{-\infty}^{\infty} t f_{X_{i-1}}(t) dt = \mu_{i-1}$. The integral of the second term can also be evaluated analytically by using $\int_{-\infty}^{\infty} u \Phi(bu + a) \phi(u) du$

$= \frac{b}{\sqrt{1+b^2}} \phi\left(\frac{a}{\sqrt{1+b^2}}\right)$ [27]. $\phi(u)$ is the probability density function of the unit normal distribution and $\Phi(u)$ is the cumulative probability function of the unit normal distribution. We introduce $u = \frac{t - \mu_{i-1}}{\sigma}$ and use $a = \frac{\mu_{i-1} - v}{\epsilon}$ and $b = \frac{\sigma}{\epsilon}$ to get the solution

$$\sigma \int_{-\infty}^{\infty} u \Phi(bu + a) \phi(u) du = \frac{\sigma^2}{\sqrt{\epsilon^2 + \sigma^2}} \phi\left(\frac{\mu_{i-1} - v}{\sqrt{\epsilon^2 + \sigma^2}}\right), \quad (\text{A4})$$

where $a = \frac{\mu_{i-1} - v}{\epsilon}$, $b = \frac{\sigma}{\epsilon}$, $\phi(u)$ is the probability density function of the unit normal distribution and $\Phi(u)$ is the cumulative probability function of the unit normal distribution. Therefore, the final solution becomes

$$\langle X_{i-1} | X_{i-1} < Y \rangle = \mu_{i-1} - \frac{\sigma^2}{\sqrt{\epsilon^2 + \sigma^2}} \phi\left(\frac{\mu_{i-1} - v}{\sqrt{\epsilon^2 + \sigma^2}}\right), \quad (\text{A5})$$

allowing us to calculate the modified mean of Eq. (A2). With this in place we have a complete framework for finding $p(\tau_1)$, the results of which are shown in Fig. 6.

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