Cell-to-cell information at a feedback-induced bifurcation point

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A ubiquitous way that cells share information is by exchanging molecules. Yet, the fundamental ways that this information exchange is influenced by intracellular dynamics remain unclear. Here we use information theory to investigate a simple model of two interacting cells with internal feedback. We show that cell-to-cell molecule exchange induces a collective two-cell critical point. We find a slow-down of critical dynamics, reflected in the dynamic exponent $z$ increasing from its well-mixed value ($z = 2$) to a two-cell collective state ($z > 2$). Finally, we show that the mutual information between the cells peaks at this critical point, and can remain large far from the critical point if the cells assume the roles of producer/consumer.

Cells sense and respond to their environment, transforming chemical cues into the modification of signaling molecules, the expression of genes, and the production of proteins. Such signaling networks are often complex, involving, among other features, multiple feedback loops. Yet, the underlying purpose of these networks is to sense and transmit information robustly. For example, in the context of immune response, the complex topology of signaling cascades in T-cells can be such that perturbing a cascade before or after a feedback loop results in dichotomous response [1]. However, coarse-graining the signaling cascade, one can define a basic unimodal-bimodal system, agnostic of biological details, which singles out a particular “readout” molecule while integrating out all others. Such coarse graining of the network results in an effective feedback term, which reduces the dynamics to a universal form near a bifurcation point [2,4]. As a result, one can apply critical scaling to these universal dynamics, modified by their non-equilibrium nature [5].

Though powerful, such analysis of intra-cellular dynamics alone treats cells in isolation, equivalent to a very dilute suspension. This ignores the role of cell-to-cell interactions, communicated by means of molecule exchange. Such communication in its simplest form involves only two cells, either similar or different, which produce, degrade and exchange a molecule. By modeling molecule exchange between two cells, with each cell a generic sense-and-secrete apparatus, one can study the fundamentals of cell-to-cell communication. Investigating the information exchange between two cells in this simple framework is the focus of this work. In what follows, we first map the generic two-cell system to effective thermodynamic coordinates; we then apply a scaling analysis of the two-cell system at its bifurcation point and find that the molecule exchange induces a slow-down of naive dynamics; and we finally quantify communication using the Shannon mutual information, which we show is maximized at the bifurcation point and can remain high away from the bifurcation point if the cells act as a coordinated pair: one a producer, the other a consumer.

Model: Within each cell, biochemical reactions in a complex signaling cascade have the net effect of producing and degrading a molecular species of interest. We specialize to dynamics that can yield either a unimodal or a bimodal molecule number distribution in steady state. Near such a bifurcation point, as was previously shown [3], the precise form of the coarse-grained feedback is irrelevant. For convenience we choose to parameterize it using Schröd’s second model [6,13], a well-studied set of reactions that minimally encodes feedback. Specifically, as illustrated in Fig. 1(a), in the first (second) cell, species $X$ ($Y$) can be produced spontaneously from bath species at rate $k_1^+$ ($q_1^+$), and can be produced nonlinearly at rate $k_2^+$ ($q_2^+$) via a trimolecular reaction involving two existing $X$ ($Y$) species and a bath species. Species $X$ ($Y$) can be degraded linearly with molecule number at a rate $k_1^−$ ($q_1^−$), or in a reaction involving three existing $X$ ($Y$) molecules at rate $k_2^−$ ($q_2^−$). In addition to the internal reactions, $X$ ($Y$) can be exchanged from the neighboring cell at rate $\gamma_{xy}$ ($\gamma_{yx}$). Physically, this can be through a gap-junction or through diffusion. We denote the number of $X$ and $Y$ molecules as $n_X$ and $n_Y$, respectively. Individually, in the absence of exchange, ($\gamma_{xy} = \gamma_{yx} = 0$), each of the two constituent cells’ molecule number distribution can be either unimodal or bimodal, depending on parameters. If exchange is switched on, ($\gamma_{xy}, \gamma_{yx} > 0$), the system converges to a collective two-cell-state, with the joint distribution un-factorizable, $P(X,Y) \neq P_X(X)P_Y(Y)$.

Thermodynamic parameters: Building upon previous work [3, 6], we construct a mapping from Schröd’s parameters to Ising-like parameters. Without exchange, the deterministic dynamics corresponding to the reactions in the left cell in Fig. 1(a) are $dx/dt = k_1^+ − k_1^− x + k_2^+ x^2 − k_2^− x^3$, where we have neglected the small shifts of $-1$ and $-2$ for large $x$. Defining the order parameter $m = (x − n_c)/n_c$, we choose $n_c$ to eliminate the term quadratic in $m$, putting the dynamics in the Landau form [6]

$$\frac{dm}{d\tau} = h − \theta m − \frac{m^3}{3}, \quad (1)$$

where we have defined $n_c = k_2^+ / 3k_2^−$, $\tau = (k_2^+)^2 t / 3k_2^−$, and $h = k_1^− / k_2^−$. The parameter $h$ is the effective interaction between the cells, characterized by the exchange rate $\gamma_{xy}$. As $h$ changes, the system undergoes a critical transition where the dynamics slows down, and this critical point can be identified by maximizing the mutual information $I_{XY}$.
two coupled cells (with k-1/R critical points [3]). Applying the same mapping to previously shown to exhibit many properties of equilibrium to high or low molecule count. The parameter \( \theta \) corresponds to \( \log P \) of the stochastic steady-state of a single cell at \( m, \theta, h \) instead of relying on the deterministic dynamics (SI Appendix). The parameter \( g \) tunes system size (molecule number) for the cell. The communication between the reaction rates and the Landau parameter \( g \) yields a bimodal marginal distribution for each cell, \( P_X(X), P_Y(Y) \). Negative \( \theta \) yields a bimodal marginal distribution for each cell, \( \theta < 0 \) for \( g = 0 \), and each cell is governed solely by its internal dynamics, \( P(X,Y) = P_X(X)P_Y(Y) \). Negative \( \theta \) yields a bimodal marginal distribution for each cell, \( \theta > 0 \). Each cell can access a broad range of accessible molecule numbers, but communication induces the cells to have nearly equal molecule number at all times. This effect is also seen when \( \theta > 0 \), in a smaller range of accessible molecule numbers.

Having established that two communicating cells undergo a bifurcation in their collective dynamics at \( \theta = 0 \), we ask: what are the properties of the two-cell bifurcation point? One can read out the mean-field critical exponents \( \beta = 1/2, \gamma = 1, \delta = 3 \) directly from the two-cell Landau form. For the exponent \( \alpha \), the single-cell system shows a minimum of its heat capacity \( C_v \) at \( \theta = 0 \) [3], with peak depth depending on the “system size” \( n_c \). Similarly, for the two-cell system, we calculate \( C_v \) directly from the empirical \( P(X,Y) \) using \( C_v = (1 + \theta) \frac{\partial^2 S}{\partial \theta^2} \) and the Shannon entropy \( S = \sum_{X,Y} P(X,Y) \ln P(X,Y) \). We plot \( C_v(\theta, n_c) \) for a range of \( n_c \) values in Fig. 2(a), confirming a minimum of \( C_v \) at \( \theta = 0 \), with \( C_v(\theta = 0) \sim n_c^{1/2} \) (inset). Therefore, at steady state, the two communicating cells near their bifurcation point are in the same mean-field universality class as the single-cell system.

At the bifurcation point, would coupling the two cells modify their individual, well-mixed dynamics? We will characterize the dynamics using the critical exponent \( \gamma \), which we proceed to extract by scaling the Renyi information. The \( n \)th Renyi entropy \( S_n(X) \) generalizes the Shannon entropy such that \( S_n(X) = \frac{1}{1-n} \ln \sum_X P^n(X) \),

\[
\begin{align*}
\frac{dm_X}{dt} &= h_X - \theta_X m_X - \frac{m_X^3}{3} + g_X (m_Y - m_X) \quad \text{(2)} \\
\frac{dm_Y}{dt} &= h_Y - \theta_Y m_Y - \frac{m_Y^3}{3} + g_Y (m_X - m_Y) \quad \text{(3)}
\end{align*}
\]

where \( g_X = 3\gamma_x k_2 / (k_2^+)^2 \) and \( g_Y = 3\gamma_y q_2 / (q_2^+)^2 \). These expressions define a mapping to characterize the exchange terms between cells.
giving Shannon’s formula when \( n \to 1 \). Accordingly, the \( n \)th Renyi information, \( R_n = S_n(x) + S_n(y) - S_n(x, y) \), when scaled by the system size, can be employed to probe the critical point in a variety of systems \([3, 18]\). Fig. 2(b) shows the \( n = 2 \) Renyi information, \( R_2(\theta) \), for identical communicating cells with \( h = 0 \) and several values of \( n_c \). From equilibrium theory we expect curve crossings of \( R_2(n_c)/L(n_c) \) at the critical point with \( L(n_c) \) the effective system size \([15]\). For finite-size equilibrium systems at their critical point, the system size \( L \) truncates the correlation length \( \xi \) such that they both scale with the correlation time \( \tau_c \) as \( L \sim \xi \sim \tau_c^{-1/2} \). Although in our biochemical model there is no obvious “length” \( L \), the correlation time is well-defined and so similarly defines an effective length \( L(n_c) \) through \( z \). Thus, to find \( z \), we proceed in two steps: (i) we characterize the correlation time of the system \( \tau_c \) as a function of the molecule number \( n_c \); (ii) we find the value of \( z \) which produces the best curve-crossing for the scaled Renyi information \( R_2(\tau_c^{1/2}) \) at \( \theta = 0 \). Fig. 2(c) shows the dependence of correlation time, \( \tau_c \), on \( n_c \), computed from Gillespie simulations with \( \theta = h = 0 \) using the method of batch means \([17]\). The two curves represent a simulation with exchange (red, \( g = 1 \)), and without it (blue, \( g = 0 \)). To find \( x \) in \( \tau_c \sim n_c^x \), in Fig. 2(d) we plot the local slope, \( x = d\ln \tau_c/d\ln n_c \), from Fig. 2(c). Without exchange, van-Kampen’s “system size” expansion shows that \( x = 1/2 \) \( [18] \), and this value is confirmed by the blue curve in Fig. 2(d). With exchange, \( x \geq 1/2 \) with \( x \to 1/2 \) as \( n_c \) increases.

We may now extract the value of \( z \) which produces the best curve crossing of \( R_2(\theta = 0, n_c)/n_c^{x/z} \). For several \( n_c \) values, varying \( x/z \), we minimize the root-mean-squared distance \( D \) between all pairs of curves \( R_2(n_c)/n_c^{x/z} \) at \( \theta = 0 \). Choosing \( M \) values of \( n_c \), labeling any two as \( n_{c,i} \) and \( n_{c,j} \), and setting \( \theta = 0 \), we define \( D = \frac{1}{M} \sqrt{\sum_{ij} \left( R_2(n_{c,i})/n_{c,i}^{x/z} - R_2(n_{c,j})/n_{c,j}^{x/z} \right)^2} \) and plot \( D \) as a function of \( x/z \) in Fig. 2(e) to obtain the best-collapse (smallest \( D \)) value of \( x/z \approx 0.2 \) (see Fig. 2(c) inset). This procedure was repeated for \( R_2, R_3, R_4 \), all of which yield the same minimal \( D \) at \( x/z \approx 0.2 \). Surprisingly, since \( x \geq 1/2 \) this implies that \( z > 2 \), a departure from the well-mixed dynamics of the single cell at the mean-field limit \([15]\). Indeed, by introducing exchange, the resulting increase of \( z \) above 2 is consistent with a slowdown of dynamics in systems with reduced dimensionality. To verify our scaling hypothesis, Fig. 2(f) shows the quantity \( R_2(n_c^{x/z}) \) plotted as a function of \( \theta \), with a clear curve crossing as expected at \( \theta = 0 \) (inset). Thus, we find that the two communicating cells fluctuate in concert, maintaining their steady-state single-cell mean-field critical exponents, but with dynamics slower \( (z > 2) \) than the equivalent single cell.

In the language of our Ising-like parameters \((h, \theta)\), what values result in the most effective cell-to-cell communication? We quantify communication by means of the Shannon mutual information, \( I \), shown in Fig. 3(a) for identical cells, with \( h = 0 \). Each curve represents a different system size, \( n_c \). As \( n_c \) increases, \( I \) peaks closer to the critical point, \( \theta = 0 \). When \( \theta < 0 \), as shown in Fig. 3(b), the deeply bimodal regime inhibits stochastic switching, reducing information exchange. Conversely, when \( \theta > 0 \), noise dominates communication, suppressing \( I \). Moreover, Figure 3(b) shows that \( I(n_c, g, \theta = 0) \sim \ln n_c^{1/4} \), to be contrasted with \( \tau_c \sim n_c^{-1/2} \), indicating a fundamental trade-off between information and response time in the system: higher precision and faster response-
We let each cell have individual values for: regimes with dissimilar cells that can communicate effectively. Generally, mutual information can be large when \( n_{cX} \neq n_{cY} \), but it remains largest when \( n_{cX} = n_{cY} \), indicating that it is not advantageous for communication to persist in different molecule-number scales. (b) Letting \( \theta_X \neq \theta_Y \), mutual information is maximized in a small region near each cell’s critical point, and drops rapidly when \( \theta_{X,Y} < 0 \), but can remain appreciable when \( \theta_{X,Y} > 0 \). (c) The internal timescale parameters, \( k_1 \) and \( q_1 \), are varied. Communication-wise, it is generally advantageous for cells to operate on a similar timescale.

Fig. 4(d) shows a surprising feature: not only is mutual information maximal at \( h_X = h_Y = 0 \), but also, strikingly, can remain large when \( h_X + h_Y \approx 0 \), in contrast to the symmetric \( h \neq 0 \) case in Fig. 4(c). The case \( h_X + h_Y \approx 0 \) models a producer-consumer pair because the field \( h \) controls baseline production \([3]\). The pair, if rates are matched, can communicate effectively. Thus, our simple model captures a ubiquitous biological scenario, showing that it supports efficient communication. 

**Discussion:** We have shown that coupling two idealized cells, can give rise to a critical system. Extending the Schögl model, and capitalizing on a mapping between the internal dynamics of each cell and the mean-field Ising model, we cast each constituent of the system in terms of Ising-like quantities. Employing a curve-crossing of the normalized Renyi information, we show that dynamics are slower than mean-field, with the exponent \( z \geq 2 \). At the collective bifurcation point, \( \theta = h = 0 \), mutual information is maximized, though dynamics are faced with a precision/response trade-off due to critical slowing down. Further, a producer-consumer pair, along the band \( h_X + h_Y \approx 0 \), supports high mutual information.

The mutual information between two cells can be directly measured from experimental data, such as fluorescence microscopy movies. As such, it is well-suited for high-throughput studies that quantify cellular communication from large-scale biological data-sets. Here, we suggest a minimal model of cell-to-cell communication and with it, a simple theoretical framework. The framework we present could be applied to translate experimental data to thermodynamic and information-theoretic quantities which are informative and interpretable.

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[1] R. M. Vogel, A. Erez, and G. Altan-Bonnet, Nature Com-
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**ISING PARAMETERS WITH STOCHASTIC CORRECTIONS**

The steady state molecule number distribution for the single-cell birth-death process with propensities

\[ b_j = k_1^+ + k_2^+ j(j-1), \quad d_j = k_1^- j + k_2^- j(j-1)(j-2) \]  

as in Fig. 1(a) is [3]

\[ p_n = p_0 \prod_{j=0}^{n-1} \frac{b_j}{d_{j+1}}, \]  

with \( p_0 \) set by normalization. The maximum, or equivalently the maximum of the log

\[ \log p_n = \log p_0 + \sum_{j=0}^{n-1} \log b_j - \sum_{j=0}^{n-1} \log d_{j+1}, \]

occurs when

\[ 0 = \frac{d \log p}{dn} = \log b_{n-1} - \log d_n, \]

where we have approximated the sums as integrals. Eq. [3] implies

\[ 0 = b_{n-1} - d_n = k_1^+ + 2k_2^+ - (k_1^- + 3k_2^+ + 2k_2^-)n + (k_2^+ + 3k_2^-)n^2 - k_2^- n^3. \]

Defining

\[ \hat{k}_1^+ = k_1^+ + 2k_2^+, \]
\[ \hat{k}_1^- = k_1^- + 3k_2^+ + 2k_2^-, \]
\[ \hat{k}_2^+ = k_2^+ + 3k_2^-, \]
\[ \hat{k}_2^- = k_2^-, \]
we see that Eq. S6 is equivalent to the steady state of the deterministic dynamics above Eq. 1 with \( k \to \tilde{k} \). Therefore, replacing \( k \to \tilde{k} \) in the expressions for \( n_c, \tau, \theta, h, \) and \( g \), and using \( m = (n^* - n_c)/n_c \) as the order parameter with \( n^* \) the mode(s) of \( p_n \), provides a more accurate mapping when molecule numbers are small.

**GAUSSIAN APPROXIMATION FOR \( h_X \neq h_Y \) CASE**

Fig. 4(d) of the main text shows a ridge in the mutual information when \( h_X + h_Y = 0 \). Here, we approximate the joint molecule number distribution as Gaussian to understand the appearance of this ridge. For a pair of Gaussian random variables with covariance matrix \( C \), the mutual information is

\[
I = \frac{1}{2} \log \left( \frac{\det C}{\det C_{xx}} \right),
\]

where \( \det C = C_{xx}C_{yy} - C_{xy}^2 \). We obtain the covariance matrix by writing down the Langevin equations corresponding to the reactions in Fig. 1(a). Specifically, we linearize the Langevin equations, which yields an Ornstein-Uhlenbeck process, whose steady state covariance matrix is known from Itô calculus to take the form \[10\]

\[
C = \int_0^\infty e^{A t} \mathbb{B} B^T e^{A^T t} dt,
\]

where

\[
A = \begin{pmatrix}
-(c_X + \gamma) & \gamma \\
\gamma & -(c_Y + \gamma)
\end{pmatrix},
\mathbb{B} = \begin{pmatrix}
\sqrt{b_X} & -\sqrt{d_X} & -\sqrt{\gamma_x} & 0 \\
0 & 0 & -\sqrt{\gamma_y} & -\sqrt{\gamma_y}
\end{pmatrix}
\]

are the linearized Jacobian and Langevin noise matrices at the mean molecule numbers \( \bar{x} \) and \( \bar{y} \), written for simplicity in terms of the total birth and death rates and their derivative,

\[
b_X(x) = k_1^+ + k_2^+ x^2, \quad d_X(x) = k_1^- x + k_2^- x^3, \quad c_X = \partial_x [d_X(x) - b_X(x)],
\]

all evaluated at \( \bar{x} \), and similarly for \( Y \) (with \( k \to q \)).

We express the rates in terms of the Ising parameters using the mapping below Eq. 1 which in the limits of Fig. 4(d) (\( n_{cX} = n_{cY} = n_c, \theta_X = \theta_Y = 0, k_1^- = q_1, g_X = g_Y \)) simplify to

\[
k_1^+ = k_1^- n_c (h_X + 1/3), \quad k_2^+ = \frac{k_1^-}{n_c}, \quad k_2^- = \frac{k_1^-}{3n_c}, \quad \gamma = k_1^- g.
\]

We express the mean molecule numbers \( \bar{x} = n_c (1 + m_X) \) and \( \bar{y} = n_c (1 + m_Y) \) in terms of the Ising order parameters, which at steady state satisfy

\[
0 = -\frac{1}{3} m_X^3 + h_X + g(m_Y - m_X),
0 = -\frac{1}{3} m_Y^3 + h_Y + g(m_X - m_Y).
\]

These equations are solved by

\[
\frac{1}{g^3} \left( \frac{m_X^3}{81} - \frac{h_X m_X^4}{9} + \frac{h_X^2 m_X^3}{3} - \frac{h_X^3}{3} \right) + \frac{1}{g^2} \left( \frac{m_X^3}{9} - \frac{2h_X m_X^4}{3} + h_X^2 m_X \right) + \frac{1}{g} \left( \frac{m_X^3}{3} - h_X m_X^2 \right) + 2 m_Y^3 - h_X - h_Y = 0.
\]

and similarly for \( X \leftrightarrow Y \). In the limit of small \( g \) the first term dominates, and we recover the single-cell expectation \( m_X = (3h_X)^{1/3} \). Conversely, in the limit of small \( m \) and \( h \) but order-one \( g \) [as in Fig. 4(d)] the last term dominates, and we obtain \( m_x = m_y = \left[ 3(h_X + h_Y) / 2 \right]^{1/3} \). Therefore

\[
\bar{x} = \bar{y} = n_c \left[ 1 + \left( \frac{3(h_X + h_Y)}{2} \right)^{1/3} \right].
\]
Inserting Eq. S15 and S18 into Eq. S14, Eq. S14 into Eq. S13, and Eq. S13 into Eq. S12 yields analytic expressions for the elements of the covariance matrix $C$. For small $h_X + h_Y$, the leading-order behavior of these elements is identical,

$$C_{xx}, C_{yy}, C_{xy} \sim \frac{2(12)^{1/3} n_c}{9(h_X + h_Y)^{2/3}}.$$  

(S19)

This means that the numerator of Eq. S11 goes like $(h_X + h_Y)^{-2/3}$, whereas in the denominator, the leading-order terms cancel. Consequently, the numerator diverges more quickly than the denominator as $h_X + h_Y \to 0$, and therefore the mutual information diverges along this line.

We do not expect the Gaussian approximation to hold precisely at the critical point $h_X = h_Y = 0$. Indeed, the mutual information does not diverge, but rather has a finite maximum near this point, i.e. the ridge in Fig. 4(d). Nonetheless, the divergence that we derive here provides an intuitive explanation for the ridge.