Subjective Information in Life Processes: A Computational Case Study

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ABSTRACT

Information processing has increasingly gained traction as a unifying and holistic concept to characterize biological systems. Current research has obtained important but limited results in applying information to understanding life, mainly because of inherent syntactic constraints embedded in a universally accepted theory, formulated for communication system engineering, rather than a universal characterization of nature. In this paper, we further the notion of "subjective information", which takes into account the relative importance of different information sources for distinct life functions. To this end, we develop a computational model of a microorganism that requires two metabolic substrates to survive and grow. The substrates have different spatial distributions, and the organism acquires information on their environmental concentrations and gradients through a noisy receptor-binding process, ultimately guiding its chemotaxis in the environment to increase the chances of growth and survival. Our simulation results reveal a trade-off between a living system's capability to maximize the acquisition of information from the environment, and the maximization of its growth and survival over time, suggesting that a form of "subjective information" promotes growth and survival in life processes, rather than the classical, purely syntactic Shannon information.

KEYWORDS

Information theory in biology, computational simulation of biological cells, cellular automata, chemical reception, mutual information.

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1 INTRODUCTION

The modern development of biological systems research has identified the need to understand living systems and their component processes from an information-centric point of view [5]. There is widespread awareness that measuring and understanding the information involved in these processes could be key to advance a common reference metric to characterize, analyze, and eventually interact with biological systems at multiple scales, ranging from the processing of information via molecular interactions within a cell, to complex codes in inter-organismal communication, and the consequent emergence of long-term evolutionary patterns.

The restriction of Shannon's mathematical theory of communication [4, 14] to purely syntactic considerations, where the *meaning* of information is considered irrelevant to the engineering problem, was a conceptual *sine qua non* for its success and applicability within communication engineering. Despite attempts to apply these concepts in biology, from neuroscience to biochemistry, and data analytics for bioinformatics, even abstracting biological systems as communication channels [2, 6, 13], the aforementioned syntactic nature of information theory provides an obstacle to its application to living systems. Intuitively, within biological systems, some messages are "more important" than others. There have been attempts to provide a quantitative basis for this idea [1, 3, 18].

Here we develop a simple but rigorous model in which the notion of "subjective information", *i.e.*, information *about* a particular subset of all the information available to an organism, emerges as a trade-off between a living system's capability to maximize the acquisition of information from the environment, and the maximization of its growth and survival over time. We show that, under certain conditions, maximizing the population growth rate requires maximizing information about specific input signal components (for example, specific metabolites), in a way that deliberately discards a larger quantity (in bits) of less useful information in favor of a smaller quantity of more useful information.

The rest of the paper is organized as follows. In § 2, we introduce a basic model of life processes exhibiting the aforementioned characteristics, based on chemical reception and chemotaxis of a microorganism, together with its computational implementation. In § 3 we evaluate the efficiency of the microorganisms in two contrasting ways: first, in terms of a classical, strictly syntactic information measure applied to acquisition of information through chemical reception, and second, in terms of its growth rate efficiency, or rate of cellular division. In § 4 we introduce and discuss numerical results generated from our simulations, as well as some details on the estimation of the performance metrics from data. Finally, we draw conclusions in § 5.

2 TWO-RESOURCE FORAGING MODEL

To develop a framework within which "subjective information" is well defined, we consider a microorganism that requires two metabolic substrates to survive and grow. The substrates have different spatial distributions, and the organism detects their local concentrations and gradients through a noisy receptor-binding process [15, 17], guiding chemotaxis [9]. One can then compare the success (in terms of growth rates [8, 12]) of strategies based either on maximizing information [19] or, alternatively, prioritizing survival at the cost of reduced information [1].

2.1 Conceptual Model Description

Consider a motile species of cells of length ℓ, inhabiting a one-dimensional environment of length $L \gg \ell$. We assume each cell consumes two distinct metabolites, A and B, both at a basal maintenance rate of metabolism S [10]; and that A and B are present in the environment at determinate concentrations in each environment location. To grow and divide, a cell must maintain a positive internal store of both A and B, by absorbing them from the environment. When both the amounts of A and B cross a threshold, the cell divides into two daughter cells each receiving half of the internal store of A and B.

Each cell navigates based on the gradient along its length of the number of bound receptors for substrates A and B. The receptors comprise four binomial channels [15, 16, 20] for A/B on the right/left end of the cell. Each cell modulates its sensitivity to the surrounding A and B distributions by allocating a fixed total number of receptors among the four types. We consider two different sensitivity strategies: (i) **equal receptor allocation**, *i.e.*, the cell allocates its receptors to be equally sensitive to both A and B in the environment, or (ii) **adaptive receptor allocation** [22], *i.e.*, the cell redistributes its receptors to bias its sensitivity towards the molecule type it needs the most for growth (and possible division) at each time instant. We compare the strategies using two metrics: information efficiency and population growth rate (cf. §3).

2.2 Computational Model

2.2.1 Discrete Environment Model. For numerical convenience, we impose periodic boundary conditions, and discretize the continuous location $x \in [0, L]$ so that each cell location $\bar{x} \in \{i\,L/N \mid i = 0, \ldots, N-1\}$. Thus $\bar{x} = 0$ ($i = 0$) and $\bar{x} = L$ ($i = N$) represent the same location. The concentrations of molecular substrates A and B, which remain fixed throughout time, are given by the von Mises distributions

$$[C]_i = [C]_{\max} \exp[\kappa_C \cos(2\pi(\bar{x}_i - \mu_C)/L)]/(L\, I_0(\kappa_C)), \quad (1)$$

where $C \in \{A, B\}$, $\mu_A = 25$ and $\mu_B = 75$, respectively, $\kappa_A = \kappa_B = 0.1$, and I_0 is the modified Bessel function of the first kind [11]. We choose the von Mises distribution because it is the maximal entropy distribution on a periodic support for a given mean and circular variance [7]. We use $[A]_{\max} = [B]_{\max} = 500$ for all simulations. The nonuniform distribution of molecules of type A and B across the environment results in a non-zero expected gradient in the number of bound receptors along a cell. Therefore cells can use chemotaxis to improve their food intake, setting the stage for a non-trivial analysis of the two sensitivity modulation strategies.

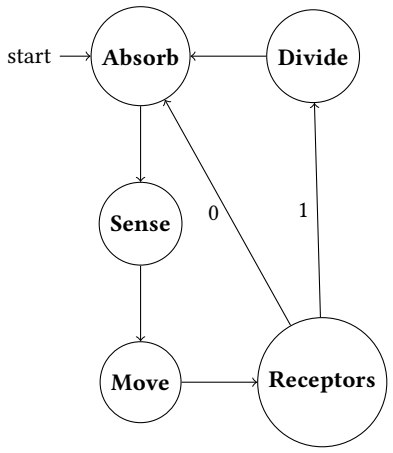

Figure 1: State machine diagram of the cell computational model formulated in this paper.

2.2.2 Cell State Machine. Fig. 1 shows the computational model for our motile cells as a state machine diagram. The state transitions include: absorption of A and B molecules, gradient sensing (estimating $\nabla[A]$, $\nabla[B]$), movement based on the estimated gradient, and sensitivity modulation via receptor reallocation. Finally, the cell divides if it has a surplus of molecule A and B that exceeds a fixed threshold, D. We next present each step in detail. See Tab. 1 for parameter values.

Absorb. The cell absorbs A and B molecules according to their external concentrations $[A]$ and $[B]$ at the left and right of the cell, $\bar{x} - \frac{\ell}{2}$ and $\bar{x} + \frac{\ell}{2}$, respectively. To compute the absorbed A (or B) molecules ΔA_{in} (or ΔB_{in}), the average of the A (or B) concentration is multiplied by an absorption factor k [21] as

$$\Delta A_{\text{in}} = \left\lfloor k \frac{[A](\bar{x} - \frac{\ell}{2}) + [A](\bar{x} + \frac{\ell}{2})}{2} \right\rfloor, \quad (2)$$

where ΔB_{in} is computed by substituting B in place of A, and the absorption factor k translates from concentration to molecules absorbed. ΔA_{in} and ΔB_{in} are then added to the internal number A_{in} and B_{in} of A and B molecules, respectively. It quantifies how easily a cell can absorb molecules.

Sense. Each A receptor at the right end of the cell binds an A molecule with probability

$$p_{\text{bind},A+} = \frac{[A](\bar{x} + \frac{\ell}{2})}{K_d + [A](\bar{x} + \frac{\ell}{2})}, \quad (3)$$

where K_d is the chemical dissociation constant of the receptor [16]. Similarly, we define the probability of binding A at the left end of the cell (at location $\bar{x} - \frac{\ell}{2}$), as $p_{\text{bind},A-}$, with analogous probabilities $p_{\text{bind},B\pm}$ for the B receptors. For simplicity, we assume the same dissociation constant for each receptor. Equation (3) assumes that the time step of the simulation is long enough that the receptors and surrounding concentration reach a steady state. If there are A_{r+} total A-receptors on the right, and A_{r-} on the left, then the number of bound A receptors on the right and left are independent binomial random variables, *e.g.*, $A_{b+} \sim \text{Binom}(A_{r+}, p_{\text{bind},A+})$. Similar expressions hold for B.

Move. The cell moves according to an estimate of the local gradient of the concentration of molecules of type A and B:

$$\Delta i = (A_{b+} + B_{b+}) - (A_{b-} + B_{b-}), \tag{4}$$

where A_{b+}, B_{b+}, A_{b-}, and B_{b-} are the number of bound A-receptors on the right part of the cell, B-receptors on the right, A-receptors on the left, and B-receptors on the left, respectively. Δi is the change in cell location, corresponding to $\Delta\bar{x} = \Delta i\, L/N$.

Receptors allocation. We compare two sensitivity modulation strategies. In the **equal receptor allocation** strategy, the cell distributes R_{total} receptors equally among four possible types: A and B, and at the right or left end of the cell. In the **adaptive receptor allocation** strategy, the cell redistributes its receptors at each time instant based on the ratio of A to B molecules internal to the cell as follows:

$$B_r = \left(R_{\text{total}} \frac{A_{\text{in}}}{A_{\text{in}} + B_{\text{in}}} \right), \tag{5}$$

where B_r ($B_{r+} = B_{r-} = B_r/2$) is the B-receptor count, and A_{in}, B_{in} are the internal A, B molecule concentrations. In this way, the cell redistributes its receptors in proportion to its relative deficit of one metabolite versus the other. For example, if the cell has fewer B than A molecules, it will move a greater portion of its receptors to receptor type B.

Divide. At each time step, the basal energetic requirement S is subtracted from both A_{in} and B_{in}. If S is larger than either A_{in} or B_{in}, then they are set to zero independently. Each cell divides if, after subtracting S, the internal molecule numbers A_{in} and B_{in} both exceed the division threshold D. We set the threshold to $D = 5S$, that is, the energetic requirement needed to go five time steps without resetting A_{in} or B_{in}. In Fig. 1, "0" and "1" represent "under the divide threshold" and "over the divide threshold", respectively.

3 PERFORMANCE METRICS

We compare the two sensitivity modulation strategies using two metrics: one based on the amount of information cells acquire from the environment, and the other based on the cell growth efficiency. The former is formulated as the average Mutual Information (MI) [4] between the input environmental concentration of A and B molecules and the output numbers of bound and unbound receptors of the two types along a cell, which are then used by the cell to estimate their gradient. The latter is expressed as the average cell division rate, which quantifies the efficiency of the cells in utilizing the resources in the environment for population growth.

Information Efficiency. The average MI (MI) of the cells in the environment is defined as

$$MI(t) = \mathbb{E}_{\text{Total \# of cells}}[MI_{cell}(t)], \tag{6}$$

where $\mathrm{E}_{\text{\# of cells}}[\cdot]$ denotes the average computed over all the number of cells present in the environment at a determinate time instant, and $MI_{cell}(t)$ is the MI of a cell, computed as follows:

$$MI_{cell}(t) = MI_{A_+,A_{b+}} + MI_{B_+,B_{b+}} + MI_{A_-,A_{b-}} + MI_{B_-,B_{b-}}, \tag{7}$$

where A_+, B_+, A_-, B_- are the environmental concentrations of molecules A or B on the right and left the cell has seen up to time t, shorthand for $[A](\bar{x} + \frac{\ell}{2})$, $[B](\bar{x} + \frac{\ell}{2})$, $[A](\bar{x} - \frac{\ell}{2})$ and $[B](\bar{x} - \frac{\ell}{2})$, respectively. To express (7), we assumed that each of the environmental concentrations and consequent number of bound receptors are independent from each other [16]. For completeness, these MI formulas are expressed as follows [4]:

$$\begin{aligned} MI_{Y,Z} &= H(Y) - H(Y \mid Z) \\ H(Y) &= \int_Y P_Y(y) \log_2 \left(\frac{1}{P_Y(y)} \right) dy \\ H(Y \mid Z) &= \int_Z P_Z(z) H(Y \mid z)\, dz \\ H(Y \mid z) &= \int_Y P_{Y|Z}(y \mid z) \log_2 \left(\frac{1}{P_Y(y \mid z)} \right) dy, \end{aligned} \tag{8}$$

where the probability distributions $P_Y(y)$, $P_Z(z)$ and $P_{Y|Z}$ are known or estimated from available data. Y is intended here to be substituted with A_+, B_+, A_-, B_-, and Z with the corresponding $A_{b+}(t)$, $B_{b+}(t)$, $A_{b-}(t)$, and $B_{b-}(t)$, respectively. $MI(t)$ takes as input the set of all external concentrations of A and B, and the corresponding set of bound A and B receptors throughout the entire simulation up until the current time step. For example, the MI_{cell} calculated for a cell at time step 200 considers the input and output at this time step and the set of inputs and outputs in the previous 199 time steps for that same cell. This was done to analyze how a single cell can sense its environment across its entire life.

Growth Rate Efficiency. In this paper, we express the average cell Division Rate ($DR(t)$) as the average number of cells experiencing a cell division within a simulation time step, expressed as follows:

$$DR(t) = \frac{1}{\text{Total \# of cells}} \left[\sum_{\text{All cells}} \mathbb{1}_{(A_{\text{in}}(t)>D)\&(B_{\text{in}}(t)>D)} \right], \tag{9}$$

where $\mathbb{1}_{(A_{\text{in}}(t)>D)\&(B_{\text{in}}(t)>D)}$ is equal to 1 only if both the internal molecule numbers $A_{\text{in}}(t)$ and $B_{\text{in}}(t)$ at time instant t are over the aforementioned threshold D, otherwise it is 0.

4 SIMULATION

The results presented in this paper are obtained by simulating the computational model expressed in §2.2 with a computer program. The simulation time is divided into time steps, and at each step each cell undergoes a cycle of its state machine, as shown in Fig. 1. The main simulation parameters, together with their description and initialization values are shown in Tab. 1. Additional choices made for this simulation are as follows.

4.1 Empirical Performance Metrics Estimation

Numerical estimation of MI. The $MI_{Y,Z}$ is estimated from the numerical results of the simulation through Algorithms 1-3 as follows. Algorithm 1 is used to approximate the entropy of a distribution from given numerical data on Y. Algorithm 2 is used to calculate the MI given discrete data on Y and Z. Algorithm 3 is used to discretize the data given by the set of corresponding external molecule concentrations and the number of bound receptors. This is required as the entropy of the external concentration distribution and the estimation of the $MI_{cell}(t)$ are heavily dependent on how this data is discretized. Here we use a static number of bins equal to 20. This simplifies the calculations and makes it so that the entropy of a distribution can be directly compared to the MI of a joint distribution.

Table 1: Simulation Parameters

Variable	Type	Description	Initialization
$A_{r+}, A_{r-}, B_{r+}, B_{r-}$	Discrete	A/B, left/right receptor count	100 receptors
A_r, B_r	Discrete	Total A/B receptor count	200 receptors
$[A](j), [B](j)$	Continuous	A/B external concentrations at location j	von Mises
$A_{b+}, A_{b-}, B_{b+}, B_{b-}$	Discrete	A/B left/right bound receptor count	0
A_b, B_b	Discrete	Total bound A/B receptors	0
R_{total}	Discrete	Total number of receptors for a cell to allocate	400 receptors
$A_{\text{in}}, B_{\text{in}}$	Discrete	Internal A and B molecule count	0
i	Discrete	Cell location	51
k	Continuous	Absorption factor	2.0
k_d	Continuous	Dissociation constant	2.0
D	Discrete	Division threshold	$5S$
S	Discrete	Survival Cost	5
K	Discrete	Number of bins	20

Algorithm 1: Entropy ($dist$)

Result: Entropy of a data set $dist$
input : **Set** of data, $dist$;
output: $entropyX$
initialize $(\_, bins) \leftarrow$ Binning($dist$, K);
$entropyX \leftarrow 0$;
for *each index* i_{bins} *in* $bins$ **do**
  $entropyX \leftarrow entropyX - bins[i_{bins}] \log_2(bins[i_{bins}])$
end

Algorithm 2: MI($dist_Y$,$dist_Z$)

Result: Estimated Mutual Information Calculation
input : Set of data $dist_Y$ Set of corresponding data $dist_Z$
output: MI
$K \leftarrow 20$;
$(boundsZ, binnedZ) \leftarrow$ Binning($dist_Z$);
$ZallData \leftarrow$ two dimensional array of size K initialized to empty arrays;
for *each index* i_{dist} *in* $dist_Y/dist_Z$ **do**
  for *each index* j_{dist} *in* $boundsZ$ **do**
    if $boundsZ[j_{dist} + 1] > Z[i_{dist}]$ **then**
      $ZallData[j_{dist}] = ZallData[j_{dist}]$ append $dist_Y[i_{dist}]$
    end
  end
end
$entropyYgivenZ \leftarrow 0$;
for *each index* i_{all} *in* $ZallData$ **do**
  $entropyYgivenZ \leftarrow entropyYgivenZ +$ Entropy($ZallData[i_{all}]$) $\cdot$ $binnedZ[i_{all}]$
end
$MI \leftarrow$ Entropy(Y) $-$ $entropyYgivenZ$;

Algorithm 3: Binning ($dist$)

Result: Array of bins containing the probability of selecting that bin
input : Set of data points $dist$
output: bin bounds $bounds$, binned data points $bins$
$min \leftarrow dist(0)$;
$max \leftarrow dist(0)$;
$\epsilon \leftarrow 0.001$;
$K \leftarrow 20$;
for *each receptor count* i_{curr} *in* $dist$ **do**
  if $dist(i_{curr}) < min$ **then**
    $min \leftarrow dist(i_{curr})$;
  else if $dist(i_{curr}) > max$ **then**
    $max \leftarrow dist(i_{curr})$;
end
$min \leftarrow min$ - ϵ;
$max \leftarrow max + \epsilon$;
$bins \leftarrow$ zero indexed array the size of K with each index initialized to 0;
$bounds \leftarrow$ zero indexed array the size of $K + 1$;
$len \leftarrow$ length($dist$);
for *each index* i_{bound} *in* $bounds$ **do**
  $bounds(i_{bound}) \leftarrow \frac{(min-max)}{K} i_{bound} + min$;
end
for *each index* i_{bin} *in* $dist$ **do**
  for *each index* j_{bin} *in* $bounds$ **do**
    if $bounds(j_{bin} + 1) > dist_Y(i_{bin})$ **then**
      $bins(j_{bin}) = bins(j_{bin}) + \frac{1}{len}$;
    end
  end
end

Algorithm 1 is used to approximate the entropy of a distribution from given numerical data on Y.

Numerical estimation of population cell growth. The estimation of the $DR(t)$ formula in (9) from the numerical results of the simulation is performed through Algorithm 4.

Algorithm 4: Cell Growth ($cell_{div}$)

Result: Population Cell growth per time step
input : **Set** of two-dimensional data, $cell_{div}$ corresponding to division events per time step (1000) per cell;
output : $cell_{growth}$
initialize $cell_{growth} \leftarrow$ array of length 1000;
for *each index* i_{grow} *in* $cell_{growth}$ **do**
  $cell_{growth}[i_{grow}]$ = average($cell_{div}[i_{grow}]$
end

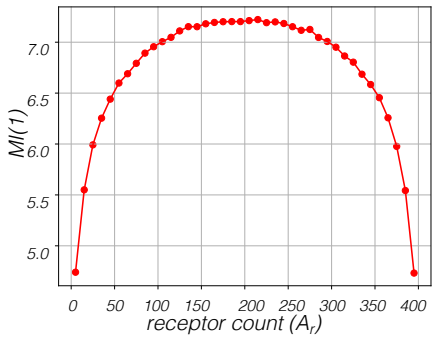

Figure 2: $MI(1)$ as function of the number of A receptors

4.2 Results

The following numerical results are obtained by running our simulation code implementation of the computational model described in §2.2 and according to the parameters and algorithms detailed in §4.1. Here we considered 100 cells for each sensitivity strategy, one at each spatial location, simulated individually in a time step increment from 0 to 100 (or 1000). In the simulation, each receptor has a certain probability p_{bind} to be bound according to (3). Each binding event is considered individually and is resolved as a realization of a binomial distribution with parameter $p_{\text{bind},A|B\pm}$. During the simulation, cell spatial distributions, corresponding division events, numbers of A and B bound receptors on the left and right part, as well as cell movement are recorded for each time step.

In Fig. 2 we show $MI(1)$, as defined in §3, for 100 cells placed equally at each location $\bar{x}$ in the environment, simulated for one single time step, as a function of the number of allocated A-receptors (the total number of receptors is constant at 400). It is noticeable that the maximum MI is obtained for an equal receptor allocation (200), which corresponds to the sensitivity strategy (i).

Figure 3 includes a joint visualization of the discrete von Mises distribution for molecules A and B, the consequent locations and division events ("x" marks) of a couple of cells as a function of the simulation time, and the resulting distribution of all the cells and cell divisions at the end of the simulation (100 time steps). The movement of cells adopting strategy (ii) is noticeable faster than those with strategy (i). The strategy (ii) results in a higher final population density than strategy (i), and it more closely resembles the shape of the von Mises distribution for molecules A and B. These results seem to suggest that the strategy (i) that would maximize MI, and therefore maximize the average information acquisition performance of the cells, results instead in lower performance in terms of final cell density, suggesting this also will reflect in the growth rate efficiency, as shown next.

In Fig. 4 and Fig. 5 we show the simulation results in terms of $MI(t)$ and growth rate efficiency, *i.e.*, $DR(t)$, as defined in §3, for sensitivity strategy (i)-top and (ii)-bottom, respectively, as function of the simulation time step, up to 1000. Strategy (i) results in a consistently higher MI, as expected from Fig. 2. The $DR(t)$ of the cells adopting strategy (i) is consistently at 0.1. This can be understood as a 10% probability of dividing for each cell at any given time step. This is lower compared to the $DR(t)$ resulting from strategy (ii), which is about twice as large, at 0.2. This confirms the **superior performance of the adaptive receptor allocation of strategy (ii) in terms of growth rate efficiency over strategy (i), even if the latter results in a higher amount of average information acquired by each cell**, as shown by $MI(t)$ estimated during 1000 simulation steps.

5 CONCLUSION

This paper presented a simple cell model to show how one may define "subjective information" in a living system. The model consisted of a periodic one-dimensional environment hosting a population of cells that can absorb molecules, sense and move in response to concentration gradients, dynamically change their sensitivity, and divide. Two cell types were analyzed, one that maximizes concentration sensitivity, strategy (i), and another that maximizes growth and division, strategy (ii). These strategies were analyzed using performance metrics of average mutual information MI, and cell population growth rate, or $DR(t)$. The average MI for the cells adopting strategy (i) is shown to be much higher than the average MI for strategy (ii). At the same time, the $DR(t)$ of the cells adopting strategy (i) was about half the growth rate seen for strategy (ii). This has shown that strategy (ii) is superior strategy in terms of growth rate efficiency, but does not correspond to the highest information acquisition capability. This simple model identifies "subjective information" intrinsic to living processes that can be used to optimize what signals a biological system, in order to grow, attempts to become more sensitive to.

A more robust model and *in vivo* experiments will be required to better define and quantify "subjective information" of a living system. With this analysis, this new information metric may identify an important aspect of biological systems that can be used in tandem with syntactic information theoretic principles.

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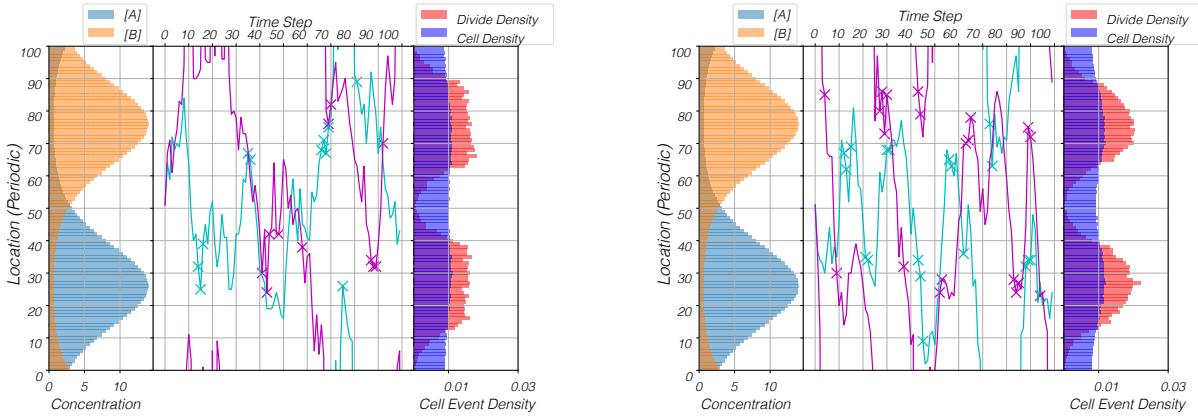

Figure 3: Joint visualizations of the environment distributions of A and B molecules, the locations and division events of two tracked cells as function of simulation time steps, and the resulting cell distribution and total divisions at the end of the simulation. (left): equal receptor allocation strategy. (right): adaptive receptor allocation strategy.

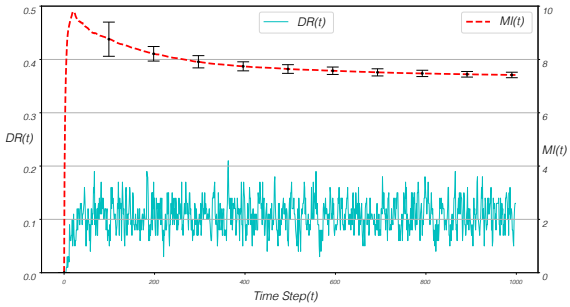

Figure 4: Estimated average mutual information $MI(t)$ and growth rate efficiency $DR(t)$ as function of the simulation time step (equal receptor allocation strategy).

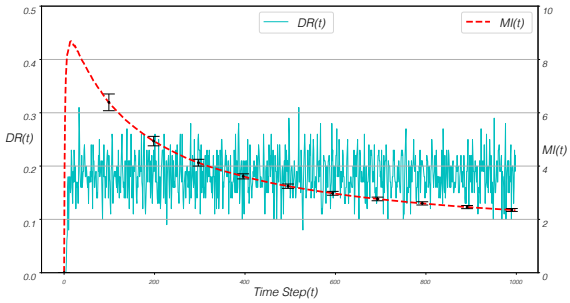

Figure 5: Estimated average mutual information $MI(t)$ and growth rate efficiency $DR(t)$ as function of the simulation time step (adaptive receptor allocation strategy).

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