Decentralized cellular timekeeping based on entropy as a regulatory mechanism for growth and aging

Jahan C. Penny-Dimri,
Monash University, Australia
{jahan.penny-dimri}@monash.edu

Abstract

The regulation of growth, aging, and lifespan share fundamental genetic and metabolic pathways. An unsolved problem for growth regulation is understanding the mechanisms through which cells, or groups of cells, coordinate when to initiate a new phase of growth, such as puberty. Here, we propose a novel mechanism called decentralized cellular timekeeping as a method by which an individual cell, as part of a network of cells, can estimate the age of the network. Decentralized timekeeping is based on a cell mapping increasing information entropy in intercellular communication to organism age. We demonstrate with a computational simulation how such a system could regulate growth.

Introduction

Developmental growth, aging and lifespan share genetic and metabolic pathways (Bartke et al., 2003; Brown-Borg and Bartke, 2012; Ma et al., 2018; Wei et al., 2013). Although much work has uncovered important developmental signals across species, little is understood about the initiation of these signals from a cell or groups of cells (Herbison, 2016; Li and Elowitz, 2019). In many situations, cells appear to have a coordinated timekeeping mechanism through which the initiation of critical phases of development are regulated. For this to be true, a candidate source of time would need to be universal across cells and applicable to heterogenous groups of cells. Information entropy of the genome is the only universal and monotonically increasing quantity in a group of cells that could be mapped to time.

The deoxyribonucleic acid (DNA) encoding the genome of each cell is exposed to a universal mutagenic force of 10^4 to 10^5 base pairs per day (Bont, 2004; Lindahl, 1993). While environmental exposures may increase or decrease the rate of mutation, DNA repair machinery can reduce it by orders of magnitude in a species specific manner (MacRae et al., 2015). Regardless of the final rate, increasing genomic information entropy from mutations is a fundamental reality for all groups of cells.

To define genomic entropy concretely we first take a base pair g from a genome, $\mathcal{G}$, as a random variable, X, and define the entropy of that base pair as

$$H_g(X) = \sum_{x \in \mathcal{X}} p(x) log(p(x)) \ , \tag{1}$$

where $\mathcal{X} = \{G, C, A, T\}$, which is the set of all possible nucleotides. The probability that the identity of the base pair is a specific nucleotide is

$$p(x) = \frac{\sum_{g}^{\mathcal{C}} \mathbb{1}_{\{x\}}(g)}{|\mathcal{C}|} \ , \tag{2}$$

where $\mathcal{C}$ is the set of all cells in the organism. The total entropy is simply the sum of $H_g(X)$ for all base pairs in the genome:

$$\mathcal{H} = \sum_{g \in \mathcal{G}} H_g(X); , \tag{3}$$

Motivation and Model Rationale

The accumulation of mutations is consistently implicated in regulating growth and lifespan across species. Genes controlling the repair of DNA double strand breaks and base excision repair are associated with early puberty (Stafuzza et al., 2019). Conversely, slower germ-line mutation rates associated with delayed puberty and increased lifespan in humans (Cawthon et al., 2020). Long-lived species have higher expression of DNA repair genes (MacRae et al., 2015). Curiously, DNA repair is also under the influence of growth hormone with deficiency causing increased DNA repair and excess hormone impairing the process (Podlutsky et al., 2017; Chesnokova et al., 2019).

The development of an organism through embryo- and morphogenesis to maturity requires a complex flow in information between cells involving many channels of communication such as gap junctions and extracellular vesicles (Levin, 2007; Cruz et al., 2018). RNA is a critical component of this information sharing system, carried in both ECVs and across gap junctions (Zong et al., 2016; Tewari, 2015). RNA is known to have an important role in regulating

gene expression and fundamentally altering cellular behavior (Cannell et al., 2008). Additionally, as a direct transcription of a cells sense and anti-sense DNA, RNA is capable of communicating the current state of a cell's genome to neighboring cells. This opens the possibility for measuring the accumulation of mutations across groups of cells.

For one mechanistic example, cells could export anti-sense fragments of RNA to neighboring cells (retaining sense), which subsequently bind to the neighbors sense RNA and suppress the expression of a particular gene or set of genes (Jose et al., 2009; Brantl, 2002). As mutations accrue in the shared RNA across the network of cells, the affinity of the anti-sense fragments to the sense decreases and expression of the gene(s) begins to increase. In this model, as the information entropy of the RNA increases in the network, gene expression increases.

Related Work

Previous work exploring aging has demonstrated the effect of evolutionary pressures on lifespan and regulatory pathways (Lindahl, 1993; Fontana and Kyriazis, 2024). No previous work has considered the question of how an individual cell could estimate the age of the organism it forms.

Model Formulation

On a 2-dimensional Cartesian plane, an organism consists of cells occupying integer coordinates. Starting with 1 cell, each cell in the organism performs a series of operations shown in Algorithm 1. The age of the organism is determined by each cell by comparing the genome of randomly selected neighbors with their own. This information is then used to regulate the growth of the whole organism - limiting its mature size.

Example Model

A working simulation was made available at https://dcte.jcpd.xyz.

Concluding Remarks

This is the first paper to propose a method of cellular timekeeping with a basis in information entropy. Critically, there is no central timekeeping source. The decentralized nature of the approach renders the system resilient to cell loss. Furthermore, we have shown how such a method of timekeeping could arise from just spontaneous genetic mutations and message passing between cells. Ongoing work needs to explore the possibility of the emergence of auto-regulatory mechanisms that map to a concept of time in complex systems.

Algorithm 1 Routine run by each cell

let a ▷ Cell estimate of genomic differences (age)
let p_m ▷ Probability of mutation at each timepoint
let $p_g : a \rightarrow [0, 1]$ ▷ Func returns probability of cell split (growth)
let $d : x, y \rightarrow \mathbb{R}$ ▷ Func returns distance of neighbor
if t = 0 **then** ▷ Initialize the first cell
  $\mathcal{G}$ = "GATTACA"
else if cell has parent **then**
  genome = copy(parent)
end if
loop
  For loop to estimate 'age'
  for neighbor ∈ cells **do**
    $a \leftarrow 0$
    $p_s \leftarrow e^{\alpha \cdot d(neighbor.x, neighbor.y)}$
    $\epsilon \sim \mathcal{U}_{[0,1]}$
    Probabilistically sample neighbors based on distance
    if $p_s > \epsilon$ **then**
      for g_i, $g_n \in$ zip($\mathcal{G}$, neighbor.$\mathcal{G}$) **do**
        if $g_i \neq g_n$ **then**
          $a \leftarrow a + 1$
        end if
      end for
    end if
  end for
  For loop to enforce mutagenesis
  for g ∈ genome **do**
    $\epsilon \sim \mathcal{U}_{[0,1]}$
    if $p_m > \epsilon$ **then**
      $g \sim \{G, C, A, T\}$
    end if
  end for
  Probabilistically determine growth based on 'age'
  $\epsilon \sim \mathcal{U}_{[0,1]}$
  if $e^{\beta \cdot a} > \epsilon$ **then**
    if unoccupied adjacent location **then**
      Clone cell to adjacent location
    end if
  end if
end loop

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