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Education

2012–2017 **Ph.D. Electrical and Computer Engineering**, *University of Delaware*, Newark, Delaware, USA, PhD Topic: Stochastic Computational System Biology.
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2009–2012 **Msc computer scientist**, *Universidad Industrial de Santander*, Bucaramanga-Santander, Colombia, *4.6/5*.
Research Topic: Studies on Objective Functions of Metabolic Networks and Flux Balance Analysis (FBA)

2003–2008 **Computer scientist**, *Universidad Industrial de Santander*, Bucaramanga-Santander, Colombia, *4.02/5*.
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Publications

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Experience

2018–present **Professor**, *Fundación Universitaria Konrad Lorenz*, Bogotá, Colombia.

2012–2018 **Research Assistant**, *University of Delaware*, Newark, Delaware, USA.

2009–Present **Research Assistant**, *High-dimensional Signal Processing Group (HDSP), Universidad Industrial de Santander*, Bucaramanga, Colombia.

2011 **Full time, Assistant Teacher.**, *Universitaria de Investigación y Desarrollo*, Bucaramanga-Santander, Colombia.
Computational Structures (Java, C++, Basic Programming), School of Systems Engineering

2011 **Research Internship**, *University of Delaware*, Newark, Delaware, USA.
Research Internship with professor Ryan Zurakowski, School of Electrical and Computer Engineering, HIV Virus Dynamics

2009–2011 **Adjunt Professor, Assitant Lecturer**, *Universidad Industrial de Santander*, Bucaramanga-Santander, Colombia.
Computational Structures (Java, C++, Basic Programming), School of Systems Engineering

2007–2011 **Research Student**, *Research Group in Biomedical Engineering* , Bucaramanga-Santander, Colombia.

Honors

- Academic excellence award, High Dimensional Signal Processing Research Group, Universidad Industrial de Santander, 2016
- Bioengineering Faculty Award, University of Delaware, Fall 2013
- Meritorious graduation work, Universidad Industrial de Santander, December 2012
- Research Assistant Scholarship, ECE, UDEL, fall 2012
- Best poster presentation in session "Functional genomics and systems biology", ISCB Latin America 2012 Conference on Bioinformatics, 2012
- Personal Support Scholarship, Universidad Industrial de Santander, 2009-2010

Leadership Activities

High Dimensional Signal Processing Research Group - Colombia

- Co-Advisor Msc Project. Finished December 2015. Grade: 4.8/5.0
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LETTER

Exact lower and upper bounds on stationary moments in stochastic biochemical systems

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Abstract

In the stochastic description of biochemical reaction systems, the time evolution of statistical moments for species population counts is described by a linear dynamical system. However, except for some ideal cases (such as zero- and first-order reaction kinetics), the moment dynamics is underdetermined as lower-order moments depend upon higher-order moments. Here, we propose a novel method to find exact lower and upper bounds on stationary moments for a given arbitrary system of biochemical reactions. The method exploits the fact that statistical moments of any positive-valued random variable must satisfy some constraints that are compactly represented through the positive semidefiniteness of moment matrices. Our analysis shows that solving moment equations at steady state in conjunction with constraints on moment matrices provides exact lower and upper bounds on the moments. These results are illustrated by three different examples—the commonly used logistic growth model, stochastic gene expression with auto-regulation and an activator–repressor gene network motif. Interestingly, in all cases the accuracy of the bounds is shown to improve as moment equations are expanded to include higher-order moments. Our results provide avenues for development of approximation methods that provide explicit bounds on moments for nonlinear stochastic systems that are otherwise analytically intractable.

1. Introduction

Stochasticity is an integral aspect of biochemical systems, in which different species are often present at low counts. Mathematical characterization of such systems is done by employing the chemical master equation (CME) [1–3]. However, the CME is analytically intractable except for few special cases, and generally requires considerable computation effort if solved numerically [4–13]. The computational cost tends to become prohibitive if one is interested in studying the long-time (i.e. stationary or steady-state) behavior of the system. Perhaps a reasonable goal is to determine a few lower-order moments (such as mean, variance, etc) of different species in the stationary state. Not only is moment computation of primary importance for many purposes, it can also be used to infer useful information about the probability density function using tools such as the Chebyshev's inequality [14], moment-based reconstruction of the probability density function [15], etc.

The time evolution of moments of a biochemical system is governed by a system of differential equations which can be obtained from the CME [16–18]. Consider a system of n species $X_j, j = \{1, 2, \ldots, n\}$ and denote the state of the system by a vector $\boldsymbol{x}(t) = [x_1(t) \quad x_2(t) \ldots x_n(t)]^\top$, where $x_j(t)$ represents the population of X_j at time t. Given a vector $\boldsymbol{m} = [m_1 \quad m_2 \quad \ldots m_n]^\top$ of n non-negative integers, a statistical moment of $\boldsymbol{x}$ is defined as $\langle x_1^{m_1} x_2^{m_2} \cdots x_n^{m_n} \rangle$, where the sum $\sum_{j=1}^{n} m_j$ is referred to as the order of the moment. Using a short-hand notation $\boldsymbol{x}^{[\boldsymbol{m}]} := x_1^{m_1} x_2^{m_2} \cdots x_n^{m_n}$, the time derivative of $\langle \boldsymbol{x}^{[\boldsymbol{m}]} \rangle$ obtained from the CME is given by [16–18]

$$\frac{\mathrm{d}\langle \boldsymbol{x}^{[\boldsymbol{m}]} \rangle}{\mathrm{d}t} = \left\langle \sum_{i=1}^{S} f_i(\boldsymbol{x})((\boldsymbol{x} + \boldsymbol{\alpha}_i)^{[\boldsymbol{m}]} - \boldsymbol{x}^{[\boldsymbol{m}]}) \right\rangle, \tag{1}$$

LETTER

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Rare cell variability and drug–induced reprogramming as a mode of cancer drug resistance

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Therapies that target signalling molecules that are mutated in cancers can often have substantial short-term effects, but the emergence of resistant cancer cells is a major barrier to full cures[1,2]. Resistance can result from secondary mutations[3,4], but in other cases there is no clear genetic cause, raising the possibility of non-genetic rare cell variability[5–11]. Here we show that human melanoma cells can display profound transcriptional variability at the single-cell level that predicts which cells will ultimately resist drug treatment. This variability involves infrequent, semi-coordinated transcription of a number of resistance markers at high levels in a very small percentage of cells. The addition of drug then induces epigenetic reprogramming in these cells, converting the transient transcriptional state to a stably resistant state. This reprogramming begins with a loss of SOX10-mediated differentiation followed by activation of new signalling pathways, partially mediated by the activity of the transcription factors JUN and/or AP-1 and TEAD. Our work reveals the multistage nature of the acquisition of drug resistance and provides a framework for understanding resistance dynamics in single cells. We find that other cell types also exhibit sporadic expression of many of these same marker genes, suggesting the existence of a general program in which expression is displayed in rare subpopulations of cells.

Melanoma, which often results from V600E mutations to the BRAF protein, is a paradigmatic example of resistance to cancer therapy. The drug vemurafenib, which inhibits the mutated BRAF protein, nearly eradicates tumours, but a small subset of cancer cells develop drug resistance[1–3].

To understand resistance at the single-cell level, we turned to cultured patient-derived melanoma cells. Cells isolated from two patients (WM989, WM983B) grown under normal conditions proliferated readily. A fractional killing dose of vemurafenib (1 μM, Extended Data Fig. 1a–d) stopped the growth of most cells, but sporadic proliferative colonies of resistant cells formed (these surviving cells' transcriptomes resembled that of drug-resistant cells in patients; Extended Data Fig. 2d). Long-term time-lapse imaging capturing the onset of resistance revealed that drug-resistant colonies can arise from single cells proliferating normally before drug addition (Supplementary Video 1; Extended Data Fig. 1f), showing that these cells are not in a dormant 'persister' state.

We considered two models for resistance in single cells: a genetic 'mutation' model and a transient, non-heritable model (Fig. 1a). In the strongly heritable mutation model, a cell in the resistant state cannot revert. In the transient model, cells transition between pre-resistant and non-resistant states, with pre-resistant cells defined as those that give rise to resistant colonies upon addition of drug (Fig. 1a). We tested these hypotheses using Luria and Delbrück's 'fluctuation analysis'[12]. First, we isolated a single cell from the parental cell line to minimize any existing genetic heterogeneity. We expanded this cell for 7–8 divisions, derived several single-cell cultures (approximately 1 million cells), then added drug and counted resistant colonies (Fig. 1a). If resistance were heritable, then occasional early transitions to resistance would propagate during expansion, leading to large numbers of resistant colonies. If, however, the pre-resistant state is transient, then all cells in any culture are equally likely to form a resistant colony, making large numbers of resistant colonies unlikely.

The lack of outliers in the distributions of number of resistant colonies was incompatible with a heritable pre-resistant phenotype. Simulations confirmed statistical significance with P values of 0.0005 and 0.0012 in WM989-A6 cells (Fig. 1b; replicates with 43 and 29 cultures) and 0.0395 for WM983B-E9 cells (WM983B-E9 data and analysis in Extended Data Fig. 3). Targeted DNA sequencing of 119 cancer-related genes revealed no new mutations in two resistant subclones (Extended Data Fig. 1e).

We then wondered whether single-cell gene expression differences marked pre-resistant cells. We first identified the transcriptional program associated with stable drug resistance in WM989-A6 and WM983B-E9 cells (clonal isolates of WM989 and WM983B, respectively) and stably resistant subclones (Fig. 1d and Extended Data Fig. 2a) via population-based RNA-sequencing, revealing marker genes (1,456 and 1,316 genes, respectively) whose expression increased in resistant cells but not upon drug administration (Extended Data Fig. 2b). We recovered well-known markers of drug resistance, including *WNT5A*[13], *AXL*[14], *EGFR*[15], *PDGFRB*[3], and *JUN*[16].

The low average marker expression in untreated cells may mask rare individual cells with high expression. We used high-throughput single-molecule RNA FISH[30] to count mRNA of selected resistance genes in thousands of cells before drug treatment. We found a population of rare cells (frequencies of 1:50 to 1:500) expressing resistance genes at high levels before drug exposure (Fig. 1c and Extended Data Fig. 4a, c; outliers remained after *GAPDH* normalization[17]). After 4 weeks of treatment with vemurafenib, resistant colonies expressed these markers at more uniformly high levels (Fig. 1e).

To see if sporadic marker gene expression marked cells that ultimately become resistant, we stained live WM989-A6 melanoma cells with antibodies targeting one of the sporadic markers (*EGFR*) and performed fluorescence-activated cell sorting (FACS), isolating the top 0.02–0.2% EGFR-stained cells. We then applied vemurafenib for 3 weeks (Fig. 1f), finding that EGFR-high cells produced 7.9 ± 0.92-fold (the indicated error is standard deviation) more resistant colonies (on average 2.4-fold larger) than EGFR-mixed cells (Fig. 1f and Extended Data Fig. 5a). RNA FISH confirmed higher resistance gene expression in EGFR-high cells[13–15] (Extended Data Fig. 5b–d).

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Biophysical Journal
Article

Biophysical Society

Analysis of Noise Mechanisms in Cell-Size Control

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ABSTRACT At the single-cell level, noise arises from multiple sources, such as inherent stochasticity of biomolecular processes, random partitioning of resources at division, and fluctuations in cellular growth rates. How these diverse noise mechanisms combine to drive variations in cell size within an isoclonal population is not well understood. Here, we investigate the contributions of different noise sources in well-known paradigms of cell-size control, such as adder (division occurs after adding a fixed size from birth), sizer (division occurs after reaching a size threshold), and timer (division occurs after a fixed time from birth). Analysis reveals that variation in cell size is most sensitive to errors in partitioning of volume among daughter cells, and not surprisingly, this process is well regulated among microbes. Moreover, depending on the dominant noise mechanism, different size-control strategies (or a combination of them) provide efficient buffering of size variations. We further explore mixer models of size control, where a timer phase precedes/follows an adder, as has been proposed in *Caulobacter crescentus*. Although mixing a timer and an adder can sometimes attenuate size variations, it invariably leads to higher-order moments growing unboundedly over time. This results in a power-law distribution for the cell size, with an exponent that depends inversely on the noise in the timer phase. Consistent with theory, we find evidence of power-law statistics in the tail of *C. crescentus* cell-size distribution, although there is a discrepancy between the observed power-law exponent and that predicted from the noise parameters. The discrepancy, however, is removed after data reveal that the size added by individual newborns in the adder phase itself exhibits power-law statistics. Taken together, this study provides key insights into the role of noise mechanisms in size homeostasis, and suggests an inextricable link between timer-based models of size control and heavy-tailed cell-size distributions.

INTRODUCTION

Unicellular organisms employ diverse control strategies to maintain size homeostasis, i.e., to ensure that they do not become abnormally large (or small) (1–6). It is well known that cells within an isoclonal population, which presumably follow identical size-control strategies, can exhibit significant cell-to-cell variation in size (7–11). Here, we systematically explore how such stochastic variation in cell size is impacted by various underlying noise sources, such as 1) noise in partitioning of volume among daughter cells during mitosis and cytokinesis (12–14), 2) random fluctuations in the cell growth rate that potentially have memory over multiple generations (15–21), and 3) stochasticity in the biomolecular processes associated with the cell cycle that generates randomness in the timing of cell-division (22–24).

A key question of interest is whether stochastic variation in cell size is more sensitive to some noise sources than others. Another related issue is to examine how this sensitivity to noise mechanisms changes across size-control strategies. We investigate these questions in the context of the recently uncovered "adder strategy" for size homeostasis. As per this strategy, division is triggered after newborn cells add (on average) a constant size to their size at birth (25–28). Assuming exponential growth in cell size over time, the adder strategy implies that larger newborns divide earlier (i.e., the constant size is accumulated in shorter time) than smaller newborns. The generality of this strategy can be underscored by the fact that it has been reported in many microbial species, such as, *Escherichia coli* (27), *Bacillus subtilis* (27), *Pseudomonas aeruginosa* (29), *Synechocystis sp.* (30), and *Desulfovibrio vulgaris Hildenborough* (31). We begin by describing the stochastic formulation of the adder model that encompasses different noise sources, consistent with findings of recent single-cell studies (15,25). Later on, this model is expanded to "the generalized adder," that encapsulates the adder, the sizer (division occurs upon reaching a size threshold), and the timer (division occurs after a fixed time from birth) paradigms of cell-cycle control (27,32).

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Compact spatio-spectral algorithm for single image super-resolution in hyperspectral imaging

Superresolución basado en una única imagen para imágenes hiperespectrales

Miguel A. Marquez[1], Cesar A. Vargas[2], and H. Arguello[3]

ABSTRACT

Hyperspectral imaging (HSI) is used in a wide range of applications such as remote sensing, space imagery, mineral detection, and exploration. Unfortunately, it is difficult to acquire hyperspectral images with high spatial and spectral resolution due to instrument limitations. The super-resolution techniques are used to reconstruct low-resolution hyperspectral images. However, traditional super-resolution (SR) approaches do not allow direct use of both spatial and spectral information, which is a decisive for an optimal reconstruction. This paper proposes a single image SR algorithm for HSI. The algorithm uses the fact that the spatial and spectral information can be integrated to make an accurate estimate of the high-resolution HSI. To achieve this, two types of spatio-spectral downsampling, and a three-dimensional interpolation are proposed in order to increase coherence between the spatial and spectral information. The resulting reconstructions using the proposed method are up to 2 dB better than traditional SR approaches.

Keywords: Hyperspectral imaging, spatio-spectral dimension, three-dimensional interpolation, hyperspectral downsampling.

RESUMEN

Las imágenes hiperespectrales (HSI) son de vital importancia en una amplia gama de aplicaciones, tales como la teledetección, imágenes espaciales, la detección y la exploración de minerales. Desafortunadamente, es difícil adquirir HSI de alta resolución espacio-espectral debido a las limitaciones de los equipos de sensado. Para obtener versiones de HSI de alta calidad se usan técnicas tradicionales de superresolución. Éstas técnicas no permiten el uso directo de la información espacial y espectral que son un factor decisivo para una óptima reconstrucción. En este trabajo se propone la implementación de un novedoso algoritmo de superresolución de una sola imagen hiperespectral. El algoritmo integra la información espacial y espectral en las HSI para realizar una estimación precisa de alta resolución. Esta integración se obtiene mediante el uso de dos tipos de muestreo espacio-espectral y un interpolador tridimensional, que permite aumentar la coherencia de la información inherente en la imagen. Las imágenes resultantes son superiores hasta 2 dB comparas con reconstrucciones obtenidas por enfoques tradicionales.

Palabras clave: Imágenes hiperespectrales, dimensión especial-espectral, interpolación tridimensional, sub-muestreo hiperespectral.

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Introduction

Hyperspectral imaging (HSI) collects a concatenation of bidimensional images that entails different wavelengths in a certain spectral range. Pixels in hyperspectral images are therefore represented by vectors whose entries correspond to the intensity in the different spectral bands. HSI enables the detection, classification, and identification of objects and features based on the spectral characteristics (Chakrabarti, 2011). HSI is an area with a significant impact in civilian and military applications including remote sensing, aerial, space imagery, natural resource exploration, farming, and astronomy (Belluco, 2006), (Borengasser, 2007), (Castrodad, 2010), (Melgani, 2004), (Underwood, 2003), (Dicker, 2006), (Turk, 1991). In all of these applications, it is important to obtain the highest resolution in the spatial and spectral dimensions. Typically, the hyperspectral spectrometers are used to capture high-resolution hyperspectral images, because these provide hundreds of narrow contiguous bands over a

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Conditions for Cell Size Homeostasis: A Stochastic Hybrid System Approach

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ABSTRACT How isogenic cell populations maintain size homeostasis, i.e., a narrow distribution of cell size, is an intriguing fundamental problem. We model cell size using a stochastic hybrid system, where a cell grows exponentially in size (volume) over time and probabilistic division events are triggered at discrete-time intervals. Moreover, whenever division occurs, size is randomly partitioned among daughter cells. We first consider a scenario where a timer (cell-cycle clock) that measures the time elapsed since the last division event regulates both the cellular growth and division rates. The analysis reveals that such a timer-controlled system cannot achieve size homeostasis, in the sense that the cell-to-cell size variation grows unboundedly with time. To explore biologically meaningful mechanisms for controlling size, we consider two classes of regulation: a size-dependent growth rate and a size-dependent division rate. Our results show that these strategies can provide bounded intercellular variation in cell size and exact mathematical conditions on the form of regulation needed for size homeostasis are derived. Different known forms of size control strategies, such as the adder and the sizer, are shown to be consistent with these results. Finally, we discuss how organisms ranging from bacteria to mammalian cells have adopted different control approaches for maintaining size homeostasis.

INDEX TERMS Adder, cell size homeostasis, moment closure, moment dynamics, sizer, stochastic hybrid systems.

I. INTRODUCTION

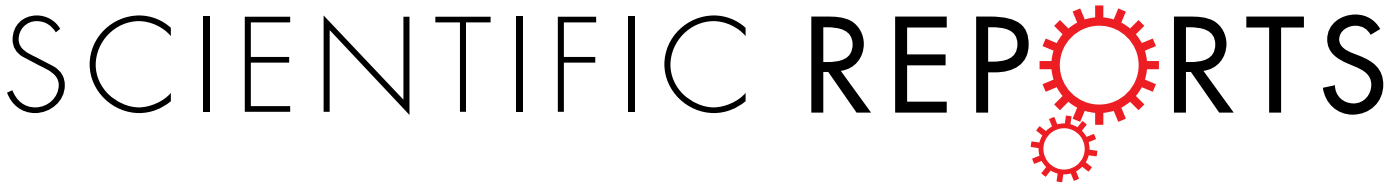
A UBIQUITOUS feature of living cells is their growth in cell size over time followed by division into daughter cells. A key question is how cells regulate their growth and timing of division to ensure that they do not get abnormally large (or small). This problem has been referred to in the literature as *size homeostasis* and is a vigorous area of current experimental research in diverse organisms [1]–[6]. We use phenomenological models of cell size dynamics based on stochastic hybrid systems (SHS) to uncover control mechanisms needed for size homeostasis. The proposed model consists of two nonnegative state variables: $\boldsymbol{v}(t)$, the size of an individual cell at time t, and a timer $\boldsymbol{\tau}$ that measures the time elapsed from when the cell was born (i.e., last cell division event). The timer can be biologically interpreted as an internal clock that regulates cell-cycle processes. Note that depending on the cell type, size can be quantified via different metrics, such as cell length in rod-shaped bacteria and cell volume/mass in mammalian cells. Time evolution of these variables is governed by the following ordinary differential equations:

$$\dot{\boldsymbol{v}} = \alpha(\boldsymbol{v}, \boldsymbol{\tau})\boldsymbol{v}, \quad \dot{\boldsymbol{\tau}} = 1 \tag{1}$$

where $\alpha(\boldsymbol{v}, \boldsymbol{\tau}) \geq 0$ is such that (1) has a unique and well-defined solution $\forall t \geq 0$ (i.e., cell size does not blow up in finite time). Since a constant α implies exponential growth over time, we refer to $\alpha(\boldsymbol{v}, \boldsymbol{\tau})$ as the *exponential growth coefficient*, while $\alpha(\boldsymbol{v}, \boldsymbol{\tau})\boldsymbol{v}$ denotes the net growth rate. As the cell grows in size, the probability of cell division occurring in the next infinitesimal time interval $(t, t + dt]$ is given by $f(\boldsymbol{v}, \boldsymbol{\tau})dt$, where $f(\boldsymbol{v}, \boldsymbol{\tau})$ can be interpreted as the *division rate*. Whenever a division event is triggered, the timer is reset to zero and the size is reduced to $\beta\boldsymbol{v}$, where random variable $\beta \in (0, 1)$ is drawn from a beta distribution. Assuming symmetric division, β is on average half and its coefficient of variation (CV_β) quantifies the error in partitioning of volume between daughters. To be biologically meaningful, $\alpha(\boldsymbol{v}, \boldsymbol{\tau})$ is a nonincreasing function, while $f(\boldsymbol{v}, \boldsymbol{\tau})$ is a nondecreasing function of its arguments. The SHS model is illustrated in Fig. 1 and incorporates two key noise sources: randomness in partitioning and timing of division. Next, we explore conditions for size homeostasis, in the sense that the mean cell size does not converge to zero and all statistical moments of $\boldsymbol{v}$ remain bounded.

II. TIMER-DEPENDENT GROWTH AND DIVISION

We begin by considering a scenario where both the exponential growth coefficient and the division rate are functions of $\boldsymbol{\tau}$, but do not depend on $\boldsymbol{v}$. The SHS can be compactly



OPEN

A mechanistic stochastic framework for regulating bacterial cell division

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How exponentially growing cells maintain size homeostasis is an important fundamental problem. Recent single-cell studies in prokaryotes have uncovered the adder principle, where cells add a fixed size (volume) from birth to division, irrespective of their size at birth. To mechanistically explain the adder principle, we consider a timekeeper protein that begins to get stochastically expressed after cell birth at a rate proportional to the volume. Cell-division time is formulated as the first-passage time for protein copy numbers to hit a fixed threshold. Consistent with data, the model predicts that the noise in division timing increases with size at birth. Intriguingly, our results show that the distribution of the volume added between successive cell-division events is independent of the newborn cell size. This was dramatically seen in experimental studies, where histograms of the added volume corresponding to different newborn sizes collapsed on top of each other. The model provides further insights consistent with experimental observations: the distribution of the added volume when scaled by its mean becomes invariant of the growth rate. In summary, our simple yet elegant model explains key experimental findings and suggests a mechanism for regulating both the mean and fluctuations in cell-division timing for controlling size.

Recurring cycles of growth and division of a cell is a ubiquitous theme across all organisms. How an isogenic population of exponentially growing cells maintains a narrow distribution of cell size, a property known as size homeostasis, has been extensively studied, e.g., see[1–4] and references therein. From a phenomenological standpoint, recent experiments reveal that diverse microorganisms achieve size homeostasis via an adder principle[5–8]. As per this strategy, cells add a constant size from birth to division regardless of their size at birth[9,10]. Interestingly, the size accumulated by a single cell between birth and division exhibits considerable cell-to-cell differences, and these differences follow unique statistical properties. For example, in a given growth condition, the added size is drawn from a fixed probability distribution independent of the newborn cell size. Moreover, the distribution of the added size normalized by its mean is invariant across growth conditions[6]. Here, we explore biophysical models that lead to the adder principle of cell size control and provide insights into its statistical properties.

To realize the adder principle mechanistically, a cell needs to somehow track the size it has accumulated since the previous division and trigger the next division upon addition of the desired size. One biophysical model proposed to achieve this assumes a protein which begins to get expressed right after cell birth at a rate proportional to instantaneous volume (size). The cell grows exponentially over time and division is triggered when protein copy numbers reach a critical threshold after which the protein is assumed to degrade (Fig. 1a)[7,10,11]. Such copy number dependent triggering of cell division could potentially be implemented via the localization of protein into compartments whose volume does not change appreciably with the cell volume[12]. Moreover, the synthesis and the degradation of the protein in this model are used in broad sense; they could as well be activation of timekeeper proteins in size dependent manner, and deactivation after triggering of division. While this deterministic model results in a constant size added from cell birth to division[10,11], it remains to be seen how noise mechanisms can be incorporated in this model to explain statistical fluctuations in cell size. A plausible source of noise could be the inherent stochastic nature of protein expression that has been universally observed in prokaryotes and eukaryotes[13–17]. Such stochasticity in protein synthesis is amplified at the level of individual cells, where gene products are often present at low molecular counts.

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RESEARCH ARTICLE

Intercellular Variability in Protein Levels from Stochastic Expression and Noisy Cell Cycle Processes

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Abstract

Inside individual cells, expression of genes is inherently stochastic and manifests as cell-to-cell variability or noise in protein copy numbers. Since proteins half-lives can be comparable to the cell-cycle length, randomness in cell-division times generates additional intercellular variability in protein levels. Moreover, as many mRNA/protein species are expressed at low-copy numbers, errors incurred in partitioning of molecules between two daughter cells are significant. We derive analytical formulas for the total noise in protein levels when the cell-cycle duration follows a general class of probability distributions. Using a novel hybrid approach the total noise is decomposed into components arising from i) stochastic expression; ii) partitioning errors at the time of cell division and iii) random cell-division events. These formulas reveal that random cell-division times not only generate additional extrinsic noise, but also critically affect the mean protein copy numbers and intrinsic noise components. Counter intuitively, in some parameter regimes, noise in protein levels can decrease as cell-division times become more stochastic. Computations are extended to consider genome duplication, where transcription rate is increased at a random point in the cell cycle. We systematically investigate how the timing of genome duplication influences different protein noise components. Intriguingly, results show that noise contribution from stochastic expression is minimized at an optimal genome-duplication time. Our theoretical results motivate new experimental methods for decomposing protein noise levels from synchronized and asynchronized single-cell expression data. Characterizing the contributions of individual noise mechanisms will lead to precise estimates of gene expression parameters and techniques for altering stochasticity to change phenotype of individual cells.

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Aplicaciones y retos del sensado remoto hiperespectral en la geología colombiana

Applications and challenges of hyperspectral remote sensing in the colombian geology

Aplicações e desafios do sensoriamento remoto hiperespectral na geologia colombiana

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César Augusto Vargas-García**
Fernando Antonio Rojas-Morales***
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Resumen

El Sensado Remoto (SR) es una técnica que permite captar información de una escena sin entrar en contacto físico con ella, mediante el empleo de sensores ubicados, principalmente, en plataformas aéreas, los cuales captan información en diferentes rangos del espectro electromagnético, incluyendo el visible (VIS), el cercano al infrarrojo (NIR) y el de ondas cortas del infrarrojo (SWIR). Teniendo en cuenta que cada material presente en una escena tiene características espectrales diferentes, es posible, a través del análisis de las firmas espectrales, realizar su identificación o clasificación mediante algoritmos. Las Imágenes Hiperespectrales (HSI) captadas por sensores remotos en cientos de bandas espectrales son de importancia en áreas como la geología, la mineralogía, la agronomía y la ecología, entre otras; sin embargo, el gran volumen de literatura dispersa en diferentes líneas (SR, HSI y geología) dificulta su acceso y análisis. Este trabajo presenta un compendio de conceptos, principios básicos y fundamentos matemáticos del SR, e incluye investigaciones y tendencias de él, destacando su desarrollo y sus retos en Colombia, y un caso de uso de HSI en la geología colombiana, cuyas evaluaciones muestran la capacidad de detección del sensor hiperespectral Hyperion, ubicado en el satélite EO-1, para el mapeo geológico en un sitio de prueba al noroccidente del municipio de Girón, departamento de Santander. Los resultados de las evaluaciones son satisfactorios; espectralmente, el coeficiente de correlación fue alto y la relación espacial entre la firma espectral obtenida y la geología conocida del área fue aceptable y correspondió al análisis de Difracción de Rayos X (DRX) realizado a muestras tomadas del área de estudio.

Palabras clave: Sensado Remoto, Imágenes Hiperespectrales, Firma espectral, Geología, Algoritmos de Detección de Objetivos.

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Conditional Moment Closure Schemes for Studying Stochastic Dynamics of Genetic Circuits

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***Abstract*—Inside individual cells, stochastic expression drives random fluctuations in gene product copy numbers, which corrupts functioning of both natural and synthetic genetic circuits. Dynamic models of genetic circuits are formulated stochastically using the chemical master equation framework. Since obtaining probability distributions can be computationally expensive in these models, noise is typically investigated through lower-order statistical moments (mean, variance, correlation, skewness, etc.) of mRNA/proteins levels. However, due to the nonlinearities in genetic circuits, this moment dynamics is typically not closed, in the sense that the time derivative of the lower-order statistical moments depends on high-order moments. Moment equations are closed by expressing higher-order moments as nonlinear functions of lower-order moments, a technique commonly referred to as moment closure. We provide a new moment closure scheme for studying stochastic dynamics of genetic circuits, where genes randomly toggle between transcriptionally active and inactive states. The method is based on conditioning protein levels on active states of genes and then expressing higher-order moments as functions of lower-order conditional moments. The conditional closure scheme is illustrated on different circuit motifs and found to outperform existing closure techniques. Rapid computation of stochasticity through closure methods will enable improved characterization and design of synthetic circuits that exhibit robust performance in spite of noisy expression of underlying genes.**

***Index Terms*—Chemical master equation, genetic circuits, moment closure, moment dynamics, stochastic gene expression.**

I. Introduction

STOCHASTICITY in gene expression creates random fluctuations (noise) in protein levels over time inside individual living cells [1]–[5]. Noise corrupts information processing in gene networks, and is detrimental for the functioning of essential proteins whose levels have to be maintained within certain bounds for optimal performance [6], [7].

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Stochastic dynamics of genetic circuits is studied using the Chemical Master Equation (CME) framework that provides the joint probability distribution for the number of molecules of the different species involved [8]–[11]. Since for most systems of interest the CME is analytically intractable, the joint pdf is computed numerically through the Finite State Projection Algorithm [12] or through Kinetic Monte Carlo methods [13]–[18] at a significant computational cost. As one is often interested in computing only a few lower-order statistical moments (for example, means, variances, correlations, skewness, etc.), much time and effort can be saved by directly computing these moments without actually having to solve for the distributions. However, nonlinearities in biochemical interactions result in the problem of moment closure: time derivative of the lower-order statistical moments depends on higher-order moments. Moments are typically solved by performing moment closure, which closes the differential equations by expressing higher-order moments as functions of lower-order moments.

Although various techniques exist for closing moment dynamics [19]–[25] they all fail when biochemical species are present at very low copy number [24], [26]. This is particularly problematic for genetic circuits, where genes switch between transcriptionally active and inactive states, and the number of active copies of a gene can be zero with high probability. One way to deal with low-copy number species is by considering conditional moments [27], [28]. Here we propose a novel closure scheme that works by first conditioning moments on genes being active, and then expressing higher-order conditional moments as functions of lower-order moments using the recently proposed derivative-matching technique [24].

The Conditional Derivative-Matching (CDM) closure method is illustrated on two network motifs in gene regulatory systems: a self-regulation gene and a two-gene circuit with a repressor and activator. Our results show that CDM provides remarkably accurate estimates of the moment dynamics across parameter regimes outperforming existing closure techniques. Finally, we discuss the applicability of CDM to the emerging field of synthetic biology both in terms of circuit design and characterization from single-cell data.

II. Model Description for a Self-Regulating Gene

Consider a gene that switches between two states: a transcriptionally active (ON) and inactive (OFF) state, with mRNA production only occurring from the ON state (Fig. 1). Let $g(t)$ be a Bernoulli random variable with $g(t) = 1$ ($g(t) = 0$) denoting that the gene is active (inactive) at time t. Assuming mRNA half-life is considerably shorter than the protein half-life, we

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INVESTIGACIÓN

A comparative study of target detection algorithms in hyperspectral imagery applied to agricultural crops in Colombia

Un estudio comparativo de algoritmos de detección de objetivos en imágenes hiperespectrales aplicados a cultivos agrícolas en Colombia

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ABSTRACT

Background: (HSI) Hyperspectral Images contain high spectral resolution information, in hundreds of contiguous bands over a specific range of the electromagnetic spectrum. In science and industry, hyperspectral information is exploited by means of classification, anomaly and target detections algorithms. Specifically, in the last two decades a wide variety of hyperspectral target detection algorithms have been proposed. However, an optimal target detection algorithm with a remarkable performance over different kinds of targets and scenarios is still an active matter of research, due to the high spectral variability and diversity of real-world scenarios.

Aim: This work presents a comparative study of target detection algorithms in hyperspectral imagery applied to agricultural crops in Colombia for evaluate performance in different scenarios.

Method: The evaluations were performed on 20 real HSI acquired by the satellite Hyperion sensor, and 6 synthetic HSI with different noise levels. 5 synthetic targets were implemented; more than 115 spectral real signatures were extracted, 11 of those signatures were used as target in the testing process, allowing to characterize 5 agricultural crops of Colombian northeastern in 5 different areas.

Results: The results show that the Adaptive Coherence Estimator (ACE) algorithm has a better performance in terms of detection probabilities $P_D > 90\%$ for different scenarios and targets of agricultural type, in both synthetic and real images.

Conclusions: In applications for target detection in HSI, it is critical to find an algorithm to have optimal performance for different scenarios and targets, due to the spectral variability generated by the geographical conditions countrywide. On the other

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Single-pixel optical sensing architecture for compressive hyperspectral imaging

Arquitectura óptica de único pixel para el sensado compresivo de imágenes hiperespectrales

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Abstract

Compressive hyperspectral imaging systems (CSI) capture the three-dimensional (3D) information of a scene by measuring two-dimensional (2D) coded projections in a Focal Plane Array (FPA). These projections are then exploited by means of an optimization algorithm to obtain an estimation of the underlying 3D information. The quality of the reconstructions is highly dependent on the resolution of the FPA detector, which cost grows exponentially with the resolution. High-resolution low-cost reconstructions are thus desirable. This paper proposes a Single Pixel Compressive Hyperspectral Imaging Sensor (SPHIS) to capture and reconstruct hyperspectral images. This optical architecture relies on the use of multiple snapshots of two time-varying coded apertures and a dispersive element. Several simulations with two different databases show promising results as the reliable reconstruction of a hyperspectral image can be achieved by using as few as just the 30% of its voxels.

----------*Keywords:* Single-pixel detector, hyperspectral imaging, compressive sensing, optical imaging, coded aperture-based systems

Resumen

Los sistemas de sensado de imágenes espectrales (CSI) capturan información tridimensional (3D) de una escena usando mediciones codificadas en dos dimensiones (2D). Estas mediciones son procesadas posteriormente por un algoritmo de optimización para obtener una estimación de la información

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ARTÍCULO DE INVESTIGACIÓN

Balance de Flujos Metabólicos en *Saccharomyces cerevisiae* basado en Compartimentalización Intracelular

Metabolic Flows Balance in *Saccharomyces cerevisiae* based on Intracellular Compartmentalization

César Augusto Vargas García[*], *Carlos Eduardo García Sánchez*[**], *Henry Arguello Fuentes*[***], *Rodrigo Gonzalo Torres Sáez*[****]

Resumen

Una de las técnicas más utilizadas para la predicción de producción de bioproductos y distribución intracelular de flujos de microorganismos es el Análisis de Balance de Flujos - FBA por sus siglas en inglés. El FBA requiere de una función objetivo que represente el objetivo biológico del microorganismo estudiado. En este trabajo se propone un nuevo tipo de funciones objetivo basada en la combinación de objetivos de compartimentos físicos presentes en el microorganismo estudiado. Este tipo de funciones objetivo son examinadas junto con un modelo estequiométrico extraído de la reconstrucción iMM904 del microorganismo *S. cerevisiae*. Su desempeño se compara con la función objetivo más usada en la literatura, la maximización de biomasa, en condiciones experimentales anaeróbicas en cultivos continuos y aeróbicas en cultivos tipo lote. La función objetivo propuesta en este trabajo mejora las predicciones de crecimiento en un 10% y las predicciones de producción de etanol en un 75% respecto a las obtenidas por la función objetivo de maximización de biomasa, en condiciones anaeróbicas. En condiciones aeróbicas tipo lote la función objetivo propuesta mejora en un 98% las predicciones de crecimiento y en un 70% las predicciones de etanol con respecto a la función objetivo de biomasa.

Palabras clave: Análisis de Balance de Flujos, FBA, iMM904, *S. cerevisiae*, Función Objetivo basada en Compartimentos.

Abstract

Flux Balance Analysis - FBA - is one of the most used techniques in prediction of microorganism bioproducts. It requires an objective function that represents biological objective of the studied microorganism. This paper presents a new kind of objective functions based on individual physical compartment objetives in the studied microorganism. These kind of functions was tested with a stoichiometric model extracted from iMM904 reconstruction of *S. cerevisiae* and its performance is compared with the most used objective function in literature, growth maximization, in anaerobic and aerobic batch conditions. The presented objective function outperform growth predictions in 10% and ethanol predictions in 75% compared with obtained by maximization of growth objective function, in anaerobic conditions. In aerobic batch conditions the presented objective function outperforms in 98% growth preditions and 70% ethanol predictions compared with growth maximization.

Key words: Flux Balance Analysis, FBA, iMM904 reconstruction, Compartment based Objective Function

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Predictive Potential of Flux Balance Analysis of *Saccharomyces cerevisiae* Using as Optimization Function Combinations of Cell Compartmental Objectives

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Abstract

Background: The main objective of flux balance analysis (FBA) is to obtain quantitative predictions of metabolic fluxes of an organism, and it is necessary to use an appropriate objective function to guarantee a good estimation of those fluxes.

Methodology: In this study, the predictive performance of FBA was evaluated, using objective functions arising from the linear combination of different cellular objectives. This approach is most suitable for eukaryotic cells, owing to their multiplicity of cellular compartments. For this reason, *Saccharomyces cerevisiae* was used as model organism, and its metabolic network was represented using the genome-scale metabolic model iMM904. As the objective was to evaluate the predictive performance from the FBA using the kind of objective function previously described, substrate uptake and oxygen consumption were the only input data used for the FBA. Experimental information about microbial growth and exchange of metabolites with the environment was used to assess the quality of the predictions.

Conclusions: The quality of the predictions obtained with the FBA depends greatly on the knowledge of the oxygen uptake rate. For the most of studied classifications, the best predictions were obtained with "maximization of growth", and with some combinations that include this objective. However, in the case of exponential growth with unknown oxygen exchange flux, the objective function "maximization of growth, plus minimization of NADH production in cytosol, plus minimization of NAD(P)H consumption in mitochondrion" gave much more accurate estimations of fluxes than the obtained with any other objective function explored in this study.

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Introduction

Gradual development on genetic manipulation techniques has opened great possibilities for alteration of microorganisms for different purposes. These approaches have ranged from improvements and developments in the production of several metabolites, to multiple biochemical and microbiological investigations [1]. Since early developments in this field, the need for global analysis of cellular systems was evident, because interaction between cellular components does not allow cell functions to be explained simply by characterizing the components comprised in it [2].

This environment led to the emergence of metabolic engineering, which is a combination of systematic analysis from different cellular networks (metabolic, signaling, etc.) with molecular biology techniques to improve cellular properties through rational design and the implementation of genetic modifications [1]. Among the areas studied by metabolic engineering, one of the most relevant fields is searching for techniques to quantitatively predict the metabolic behavior of microorganisms under different conditions. In this category, the most widely used mathematical modeling approach has been flux balance analysis (FBA) [3].

FBA is based on the assumption that evolutionary pressure has led to the redirection of cellular metabolic fluxes, seeking for an optimal distribution according to a certain cellular goal [4]. This assumption make it possible to solve (i.e. to find a flux distribution based on) the underdetermined system that results from a mass balance in steady state of the intracellular metabolites [3], shown in equation (1), transforming the issue into the optimization problem of the equation (2).

$$S * \vec{v} = 0 \tag{1}$$

ARTÍCULO DE INVESTIGACIÓN

Predicción a escala genómica de componentes de *Saccharomyces cerevisiae* mediante análisis de balance de flujos

Prediction of genome scale of *Saccharomyces cerevisiae* by flux balance analysis

César Augusto Vargas García[*], *Henry Arguello Fuentes*[**], *Rodrigo Gonzalo Torres Sáez*[***]

Resumen

El microorganismo *Saccharomyces cerevisiae* cuenta con gran número de modelos biológicos conocidos como reconstrucciones, las cuales pueden ser a escala genómica. De estas reconstrucciones a escala genómica provienen los modelos matemáticos, también llamados modelos estequiométricos. Una de las técnicas más usadas para estudiar estos modelos es el Análisis de Balance de Flujos (FBA). El proposito del FBA es predecir el crecimiento del microorganismo bajo estudio, y la producción y consumo de componentes como el etanol, CO_2, glicerol, sucinato, acetato y piruvato. Para determinar si las predicciones obtenidas mediante FBA son únicas se utiliza la técnica de Análisis de Variabilidad Flujos (FVA). El presente trabajo muestra los resultados de aplicar el FBA a la reconstrucción reciente del microorganismo *S. cerevisiae*, la denominada iMM904 y los compara con un conjunto de datos experimentales presente en la literatura. Este trabajo también estudia la existencia de múltiples predicciones FBA utilizando la técnica FVA. Los resultados ilustran que es posible predecir el crecimiento del microorganimo *S. cerevisiae*, con errores entre el 11% y 28%; la producción de CO_2, con errores entre el 0.3% y 4.5% y la producción de etanol, con errores entre el 11% y 13%.

Palabras clave: analisis de balance de flujos, reconstrucción a escala genómica, iMM904, *S. cerevisiae*.

Abstract

Several biological models, named reconstructions, are used for the study of the *S. cerevisiae* microorganism. The reconstructions can be genomic scaled. Mathematical models are generated from the reconstructions and they are called stoichiometric models. The flux balance analysis (FBA) is one of the tools used for the analysis of these models. The FBA attempts to predict the evolution of the microorganism and the consumption and production of components like glucose, ethanol, glycerol, succinate, acetate and pyruvate. A Flux variability analysis (FVA) is used to determine the uniqueness of the FBA predictions. This paper shows the results of applying FBA to the iMM904 reconstruction of *S. cerevisiae* and compares them with experimental data from literature. The results in this paper show that it is possible to predict the evolution with errors between 11% and 28% ; the production of CO_2 with errors between 0.3% and 4.5%; and the production of ethanol with errors between 11% and 13%, using FBA for the iMM904 model.

Keywords: flux balance analysis, genome scale reconstructions, iMM904, *S. cerevisiae*.

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