Banff International Research Station

for Mathematical Innovation and Discovery

Mathematical tools for evolutionary systems biology (13w5080)
Sunday, May 26-Friday, May 31, 2013

MEALS

*Breakfast (Buffet): 7:00 – 9:30 am, Sally Borden Building, Monday – Friday
*Lunch (Buffet): 11:30 am – 1:30 pm, Sally Borden Building, Monday – Friday
*Dinner (Buffet): 5:30 – 7:30 pm, Sally Borden Building, Sunday – Thursday
Coffee Breaks: As per daily schedule, in the foyer of the TransCanada Pipeline Pavilion (TCPL)
***Please remember to scan your meal card at the host/hostess station in the dining room for each meal.**

MEETING ROOMS

All lectures will be held in the lecture theater in the TransCanada Pipelines Pavilion (TCPL). An LCD projector, a laptop, a document camera, and blackboards are available for presentations.

SCHEDULE

Sunday

16:00	Check-in begins (Front Desk – Professional Development Centre - open 24 hours)
17:30-19:30	Buffet Dinner
20:00	Informal gathering in 2nd floor lounge, Corbett Hall Beverages and small assortment of snacks are available on a cash honor system.

Monday - Emphasis Evolution

7:00-8:30	Breakfast
8:30-9:30	Introduction and Welcome by BIRS Station Manager, TCPL
9:30	Andrew Clark
10:00	Lin Chao
	Coffee Break, TCPL – available from 10:30 am - 11:00 am
11:00	Michael Laessig
11:30	Daniel Fisher
12:00	Elhanan Borenstein
12:30-13:30	Lunch
13:30-17:00	Informal Discussion
	Coffee Break, TCPL – available from 2:00 pm - 3:30 pm
17:45	Thomas MacCarthy/Aviv Bergman
18:15	Fiona Chandra
18:45-19:30	Dinner

Tuesday – Emphasis Fitness Landscapes & Optimality

7:00-8:30	Breakfast
8:30	Laurence Loewe
9:00	Sergey Gavrilets
9:30	Paul Joyce
10:00	Alan Moses
	Coffee Break, TCPL – available from 10:30 am - 11:00 am
11:00	Ilya Nemenman
11:30	Michael Savageau
12:00	Kerry Geiler-Samerotte
12:30-13:30	Lunch
13:30	Guided Tour of The Banff Centre; meet in the 2nd floor lounge, Corbett Hall
14:00	Group Photo; meet in foyer of TCPL (photograph will be taken outdoors so a jacket might be required).

13:30-17:00 Informal Discussion
Coffee Break, TCPL – available from 2:00 pm - 3:30 pm
17:45 Ishay Ben-Zion
18:15 Discussion session
18:45-19:30 Dinner

Wednesday – Emphasis Networks & Robustness

7:00-8:30 Breakfast
8:30 Ryan Gutenkunst
9:00 Anton Crombach
9:30 Arno Steinacher
10:00 Joanna Masel
Coffee Break, TCPL – available from 10:30 am - 11:00 am
11:00 Nicolas Buchler
11:30 Jianzhi Zhang
12:00 Joao Xavier
12:30-13:30 Lunch
13:30-17:00 Informal Discussion
Coffee Break, TCPL – available from 2:00 pm - 3:30 pm
17:45 Daniel Charlebois
18:15 Erik van Nimwegen
18:45-19:30 Dinner

Thursday – Emphasis Modelling & Optimality

7:00-8:30 Breakfast
8:30 Linda Petzold
9:00 James Faeder
9:30 David Anderson
10:00 Michael Ferris
Coffee Break, TCPL – available from 10:30 am - 11:00 am
11:00 Sander van Doorn
11:30 Frank Bruggeman
12:00 Rosalind Allen
12:30-13:30 Lunch
13:30-17:00 Informal Discussion
Coffee Break, TCPL – available from 2:00 pm - 3:30 pm
17:45 Lindi Wahl
18:15 Scott Rifkin
18:45-19:30 Dinner

Friday – Future Perspectives

7:00-8:30 Breakfast
8:30 David Liberles
9:00 Kurt Ehlert
9:30 Mariana Gomez-Schiavon
10:00 Peter Swain
Coffee Break, TCPL – available from 10:30 am - 11:00 am
11:00 Discussion: Perspectives for evolutionary systems biology
12:30-13:30 Lunch

Checkout by 12 noon.

** 5-day workshop participants are welcome to use BIRS facilities (BIRS Coffee Lounge, TCPL and Reading Room) until 3 pm on Friday, although participants are still required to checkout of the guest rooms by 12 noon. **

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Are metabolic pathways optimal?

Steven J. Court, Bartlomiej Waclaw and ***Rosalind J. Allen***

School of Physics and Astronomy, University of Edinburgh, UK

Abstract

The core metabolic pathways that are central to the function of living organisms are remarkably conserved across all domains of life. Is this because they are optimal solutions to an evolutionary problem, or simply because they happened to evolve by chance, very early in the history of life on Earth? We have developed a computational algorithm that allows us to search for all possible alternatives to existing core metabolic pathways and test their feasibility. Applying this approach to the trunk pathway of glycolysis and gluconeogenesis, we find evidence that the existing versions of these pathways produce optimal metabolic fluxes under physiologically relevant intracellular conditions.

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Stochastic representations for jump processes in systems biology with applications to numerical methods

David F. Anderson

Department of Mathematics, University of Wisconsin - Madison

Abstract

The simplest stochastic models of biochemical processes treat the system as a continuous time Markov chain with the state being the number of molecules of each species and with reactions modeled as possible transitions of the chain. I will develop the relevant mathematical representations for the processes and then show how different computational methods can be developed and analyzed by utilizing the stochastic representations. Topics discussed will be a subset of: model development, approximation techniques, and variance reduction for Monte Carlo methods.

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Design principles of altruistic behavior

Ishay Ben-Zion, *Avigdor Eldar*

Department of Molecular Microbiology & Biotechnology, Tel Aviv University, Tel Aviv, Israel

Abstract

Many theoretical studies in the last 50 years have tried to explain the evolutionary maintenance of altruistic behavior in the face of exploitive cheaters. It is well known that a strong population structure is crucial for the maintenance of altruistic cooperation. However, it is unclear how this requirement is affected by the regulatory structure of the cooperative trait. The aim of this work is to examine the role of feedback regulation in maintaining cooperation in a public goods model. For this purpose, we introduced feedback regulation into adaptive dynamics framework, to look for evolutionarily stable regulatory strategies. Our results suggest an important advantage of positive feedback regulation over negative or no feedback: a positive-feedback structure promotes cooperation in weaker population structures as well, thus relieving a major limitation of explaining altruism. These results demonstrate that social traits may have different design principles than non-social traits. Moreover, since bacterial cooperative traits are often feedback-regulated through sensory mechanisms, elucidating the role of feedbacks may lead to experimentally amenable predictions.

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Epigenetics decouples mutational: from environmental robustness. Did it also facilitate multicellularity?

Aviv Bergman[1] and **Thomas MacCarthy[2]**

[1]Albert Einstein College of Medicine
[2]SUNY Stony Brook

Abstract

The evolution of ever increasing complex life forms has required innovations at the molecular level in order to overcome existing barriers. For example, evolving processes for cell differentiation such as epigenetic mechanisms facilitated the transition to multicellularity. At the same time, studies using gene regulatory network models, and corroborated in single-celled model organisms, have shown that mutational robustness and environmental robustness are correlated. Such correlation may constitute a barrier to the evolution of multicellularity since cell differentiation requires sensitivity to cues in the internal environment during development. To investigate how this barrier might be overcome we used a gene regulatory network model which includes epigenetic control based on the mechanism of histone modification via Polycomb Group Proteins, which evolved in tandem with the transition to multicellularity. Incorporating the Polycomb mechanism allowed decoupling of mutational and environmental robustness, thus allowing the system to be simultaneously robust to mutations while increasing sensitivity to the environment. In turn, this decoupling facilitated cell differentiation which we tested by evaluating the capacity of the system for producing novel output states in response to altered initial conditions. In the absence of the Polycomb mechanism the system was frequently incapable of adding new states, whereas with the Polycomb mechanism successful addition of new states was almost certain. The Polycomb mechanism, which dynamically reshapes the network structure during development as a function of expression dynamics, decouples mutational and environmental robustness, thus providing a necessary step in the evolution of multicellularity.

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Reverse Ecology of Microbes and Microbiomes

Elhanan Borenstein

Department of Genome Sciences, University of Washington, Seattle, WA
Department of Computer Science and Engineering,
University of Washington, Seattle, WA
Santa Fe Institute, Santa Fe, NM

Abstract

The structure of complex biological systems reflects not only their function but also the environments in which they evolved and are adapted to. Reverse Ecology — an emerging new frontier in Evolutionary Systems Biology — aims to extract this information and to obtain novel insights into an organism's ecology. This Reverse Ecology framework facilitates the translation of high-throughput genomic data into large-scale ecological data, and has the potential to transform ecology into a high-throughput field. In this talk, I will describe our work in Reverse Ecology, demonstrating how system-level analysis of complex biological networks can be used to predict the natural habitats of poorly characterized microbial species, their interactions with other species, and universal patterns governing the adaptation of organisms to their environments. I will further demonstrate the application of this Reverse Ecology framework to the study of microbial communities and specifically, to the study of the human microbiome — the diverse and complex set of microorganisms that populate the human body. I will finally discuss future directions and potential applications of this approach in medicine, biotechnology, and environmental engineering.

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Optimal metabolic states for maximization of specific growth rate

FJ Bruggeman, *Meike Wortel, Evert Bosdriesz, Anne Schwabe, Douwe Molenaar, Bas Teusink*

Abstract

When cells compete for limiting nutrients, selection favors cells that grow faster than their competitors. This principle applies to microorganisms in the wild, including pathogens, and cancer cells. With existing methods, i.e. flux balance analysis, the amount (i.e. yield) of cells that can be obtained from available nutrients can be predicted from the entire metabolic network stoichiometry of a cell. The cellular growth rate cannot be predicted from these methods. The problem is that this prediction requires the complete kinetic information of the metabolic enzymes, which we currently do not have. I will present several fundamental properties of the optimal metabolic states that maximize the specific growth rate of a cell. We have proved that regardless of the wiring of the metabolic network, its enzyme kinetics and allosteric regulation, the optimal metabolic states are always the simplest steady-state routes through the metabolic network, called elementary flux modes (EFMs). Remarkably, those routes are defined on the basis of reaction stoichiometry alone, and not from kinetics; yet they are the optimal paths for kinetic models of metabolism. Next, I will show that the maximization of the specific growth rate is achieved by the EFM that requires the least amount of enzyme. The calculation of the optimal enzyme and metabolite concentrations requires solving a limited set of algebraic relationships. This theory paves the way for the optimisation of genome-scale models of metabolism that in addition to stoichiometry incorporate enzyme kinetic information. Interestingly, EFMs are the optimal routes for maximization of fitness under batch as well as chemostat growth conditions, even though the selection pressures are different. Using optimization theory, I will show some of the general principles of the distribution of fitness control by enzymes and the enzyme fitness landscapes for those cultivation methods given biochemical, energetic, and physical constraints on cell growth. All these results apply to populations of organisms engaged in balanced, exponential growth. I will make an attempt to link the evolutionary theory for the mean specific growth rate to the evolution of the probability distributions for the interdivision times and enzyme levels that exert a high influence on fitness. Lastly, I will discuss how our findings impact the understanding of switches between qualitatively different metabolic modes and the evolution of cellular metabolism.

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Marching to the cell-cycle drum beat: Entrainment of a synthetic oscillator in budding yeast

Nicolas Buchler[1-4], *Sargis Karapetyan*[2-4], *Heungwon Park*[2-4],

Department of Biology[1], *Department of Physics*[2], *Institute for Genome Sciences & Policy*[3], *Duke Center for Systems Biology*[4]

Abstract

We have built a synthetic two-gene oscillator in budding yeast using a transcriptional activator and inhibitor pair. The gene circuit topology is similar to the core motif commonly found in circadian clocks. We measured gene dynamics in single cells with fluorescent protein reporters and timelapse microscopy. Our synthetic oscillators have the same period as the cell cycle across a wide range of growth conditions. To distinguish whether our synthetic oscillator was driven by the cell cycle or entrained by it, we blocked the yeast cell cycle using mating pheromone or nocodazole. In both cases, gene oscillation persisted with an intrinsic period similar to the cell cycle. This suggests that our two-gene oscillator can function autonomously. However, in the presence of the cell cycle, its similar period and unknown coupling leads to strong entrainment. As a point of contact with the BIRS workshop, we welcome methods of analysis compatible with our data (e.g. gene oscillation and coupling in single cells) that can evaluate the "quality" of the oscillation, elucidate entrainment conditions, and perhaps reveal modes or mechanisms of coupling.

We have also measured the expression of constitutive genes to understand how and where a synthetic oscillator might couple to the cell cycle. Using power spectral analysis, we showed that the cell-cycle drumbeat persists, even in constitutively expressed genes. Several possible explanations include cell-cycle oscillations in growth rate and DNA synthesis. Strikingly, we have also shown that the cell-cycle drumbeat occurs in fission yeast and bacteria. This suggests that cell-cycle entrainment could be a widespread and generic phenomenon.

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Limits and Tradeoffs in Autocatalytic Systems

Fiona Chandra

California Institute of Technology

Abstract

Despite the complexity of biological networks, we find that certain common architectures govern network structures. These architectures impose fundamental constraints on system performances and create tradeoffs that the system must balance in the face of fluctuating environment. This means that while a system may be optimized through evolution, the optimal achievable state must follow these constraints. One such constraining architecture is autocatalysis, seen in many biological networks including glycolysis and ribosomal protein synthesis. Using a minimal model, we show that the ATP autocatalysis in glycolysis imposes stability and performance constraints and that the experimentally well studied glycolytic oscillations are in fact a consequence of a tradeoff between error minimization and stability. We also show that additional complexity in the network results in increased robustness. Ribosome synthesis is also autocatalytic where ribosomes must be used to make more ribosomal proteins. When more ribosomes are devoted to making ribosomal proteins instead of other proteins, the autocatalysis is increased. We show that this autocatalysis also constrains system's performance and that there is in ideal range of proportion of ribosomes devoted to ribosomal proteins.

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Evolution of the damage load and the uni-cellular origin of biological aging

*Camilla U. Rang, Annie Y. Peng, and **Lin Chao***

Abstract

Deleterious mutations appearing in a population increase in frequency until stopped by natural selection. The ensuing equilibrium creates a stable frequency of deleterious mutations or the mutational load. Here I develop the comparable concept of a damage load, which is caused by harmful non-heritable changes to the phenotype. A damage load also ensues when the increase of damage is opposed by selection. The presence of a damage load favors the evolution of asymmetrical transmission of damage by a mother to her daughters. The asymmetry is beneficial because it increases fitness variance, but it also leads to aging or senescence. A mathematical model based on microbes reveals that a cell lineage dividing symmetrically is immortal if lifetime damage rates do not exceed a threshold. The evolution of asymmetry allows the lineage to persist above the threshold, but the lineage becomes mortal. In microbes with low genomic mutation rates, it is likely that the damage load is much greater than the mutational load. In metazoans with higher genomic mutation rates, the damage and the mutational load could be of the same magnitude. A fit of the model to experimental data shows that Escherichia coli cells experience a damage rate that is below the threshold and are immortal under the conditions examined.
The model estimates the asymmetry level of E. coli to be low but sufficient for persisting at higher damage rates. The model also predicts that increasing asymmetry results in diminishing fitness returns, which may explain why the bacterium has not evolved higher asymmetry.

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Modeling & Simulation of Cellular Population Dynamics: The Case for Noise-Mediated Drug Resistance

Daniel A. Charlebois[a,b] *and Mads Kaern*[a,b,c]

a) Department of Physics, University of Ottawa, Canada
b) Ottawa Institute of Systems Biology, University of Ottawa, Canada
c) Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa Canada

Abstract

Noisy gene expression can have important fitness consequences for a cell population under stress[1,2,3]. Obtaining exact analytical solutions to equations describing the complex interplay between genes, drugs, and population dynamics is often not feasible. Over the past few years our lab has developed population dynamics algorithms to simulate these scenarios[4,5]. Using these algorithms, we have found that the relaxation time scale of gene expression noise, and gene network topology, can facilitate the development of drug resistance independent of mutation[6].

1. M. Kaern, T. Elston, W. Blake, J. Collins, Nat. Rev. Genet. **6**, 451 (2005)
2. M.S. Samoilov, G. Price, A.P. Arkin. Sci. STKE, 2006
3. D. Fraser, M. Kaern. Mol. Microbiol. **71**, 1333 (2009)
4. D.A. Charlebois, J. Intosalmi, D. Fraser, M. Kaern, Commun. Comput. Phys. **9**, 89 (2011)
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6. D.A. Charlebois, N. Abdennur, M. Kaern, Phys. Rev. Lett., **107**, 218101 (2011)

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Evolutionary inference from discrete generation pooled sequence data.

Andrew Clark

Cornell University

Abstract

Sequencing pools of individuals allows a rapid and inexpensive way to assess allele frequency changes over successive generations of natural or artificial selection. A null model for this process is a set of correlated Wright-Fisher processes, where the correlation depends on local rates of recombination. With replicate populations, the Wright-Fisher model makes explicit predictions about the increase in variance among replicates over time. Departures from this null model may reflect heterogeneity in the parameters of a more complex but still neutral model, or they may reflect the action of selection. Data from an experiment in which four replicate control populations of about 10,000 Drosophila were contrasted to four replicate populations undergoing selection for starvation response. Simple methods identify regions of the genome that change in a way that is consistent across replicates. Fitting the correlated Wright-Fisher model using methods from signal processing has even greater sensitivity to identify exceptional genomic regions, and produces a richer insight to the true dynamical model for neutral variation.

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Reverse Engineering the Evolution of a Developmental Gene Regulatory Network

Anton Crombach, *Karl R Wotton, Damjan Cicin-Sain, Johannes Jaeger*

EMBL/CRG Research Unit in Systems Biology, Centre for Genomic Regulation (CRG) and Universitat Pompeu Fabra (UPF), Barcelona, Spain

Abstract

We are performing a comparative, systems-level study of the gap gene network, involved in patterning in the early embryo, across three species of diptera (flies, midges and mosquitoes): the fruit fly *Drosophila*, the scuttle fly *Megaselia abdita*, and the moth midge *Clogmia albipunctata*. For the embryo of *Drosophila* we have one of the best descriptions of how interactions between genes, proteins and other molecules generate a fully functional organism. Using this knowledge, and with mRNA-based spatial gene expression data on two other fly species, *Clogmia* and *Megaselia*, we apply a reverse engineering approach (the gene circuit method) to infer the gene regulatory networks that best describe the first phases of spatial and temporal development. Comparative analysis of these gap gene networks allows us to identify both conserved mechanisms and evolutionary changes in the regulatory interactions. In addition, we perform evolutionary simulations (*in silico* evolution) to investigate possible transitions between the networks in different flies. This allows us to predict which specific regulatory changes can account for the observed differences in gap gene expression between species, and to assess whether the evolution of gap genes is constrained by the regulatory topology of the network. Bridging the gap between experimental and theoretical approaches will enable us to understand the evolutionary dynamics that shape the control of positional information in insect embryos in a novel manner, and at unprecedented detail.

References:
1. Jaeger J, Crombach A (2012) Life's Attractors. *In: Evolutionary Systems Biology, 93-119*
2. Crombach A, et. al. (2012) Efficient Reverse-Engineering of a Developmental Gene Regulatory Network. *PLoS Comp Biol 8 (7), e1002589*
3. Crombach A, et. al. (2012) Medium-Throughput Processing of Whole Mount In Situ Hybridisation Experiments into Gene Expression Domains. *PloS One 7 (9), e46658*

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Bridging Scales when Modeling the Evolution of Disease

Troy Day

Queen's University
Kingston, Canada

Abstract

I will present some theoretical results that link within-host dynamics of pathogen replication to between host epidemiological and evolutionary dynamics. One of the main novelties of the approach I will present lies in its ability to make short-term evolutionary predictions about disease life history evolution that account for populations not at evolutionary or epidemiological equilibrium. The core ingredients of the approach are genetic covariance functions for epidemiological parameters over the course of an infection. I will illustrate the approach with an example taken from research on malaria.

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Lazy Updating increases the speed of stochastic simulations

Kurt Ehlert *and Laurence Loewe*

Laboratory of Genetics and Wisconsin Institute for Discovery at the University of Wisconsin-Madison

Many biological reaction networks contain molecules involved in many reactions. For example, ATP is often consumed or produced. When reaction networks contain molecules like ATP, they are difficult to efficiently simulate, because every time such a molecule is consumed or produced, many propensity updates need to occur. In order to increase the speed of simulations, we developed the "Lazy Updating" method, which postpones propensity updates. Lazy Updating can be used in conjunction with many stochastic simulation algorithms, including Gillespie's direct method and the Next Reaction Method.

We tested Lazy Updating on two example systems and found that it substantially increased the speed of simulations. We derived a formula predicting the expected speed increase and showed that the empirical speed increase matches our expectation closely. According to our results, Lazy Updating trades off a small amount of accuracy for a large speed increase. Since Lazy Updating enhances our ability to quickly simulate large reaction networks, it is a useful add-on to existing stochastic simulation algorithms.

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Energy Lasso: Combining Rule-Based Modeling and Bayesian Parameter Estimation to Infer Biochemical Mechanisms

*Justin S. Hogg and **James R. Faeder***

Department of Computational and Systems Biology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania USA

Abstract

Rule-based modeling (RBM) is a modular and scalable approach to specifying and simulating large-scale models of cell regulatory networks. How can such models be related to experimental data and, more importantly, used to make mechanistic inferences?

We start by presenting a generalized form of the thermodynamic rule-based modeling called energy BioNetGen Language (eBNGL), which builds on work of Ollivier and Swain and of Danos and colleagues. The key idea is that cooperative effects between sites of transformation (e.g., binding and post-translational modification) can be encoded as energy parameters, which, when non-zero, introduce variation in the rates of reaction over the initial reaction classes. In RBM each rule serves as a generator of a specific class of chemical transformation, e.g., a non-covalent bond between two sites of different proteins or a posttranslational modification of a particular site, and all reactions generated by a rule inherit the same rate constant. eBNGL allows this assumption to be relaxed and permits systematic investigation of cooperativity parameters. Although these parameters cannot typically be measured, pioneering work by Sethna and colleagues has shown that biochemical models typically exhibit a characteristic known as “sloppiness,” which is a wide dynamic range in the sensitivity of a model’s behavior to its input parameters. This property has the counterintuitive effect that even models that have many parameters that are poorly constrained by data can yield relatively tight behavioral predictions. Furthermore, mechanistic inferences may be made on the basis of the subset of parameters that are tightly constrained. Work by a number of groups has shown that Bayesian parameter estimation techniques perform well in parameterizing such complex models, carrying out model selection, and inferring mechanisms.

We have coupled eBNGL and Bayesian parameter estimation with the goal of identifying cooperative mechanisms in signal transduction networks. Model selection is performed by introducing L1-regularization – aka LASSO – which holds cooperativity parameters to a zero value unless evidence suggests otherwise. We apply this approach to Kholodenko’s data on phosphorylation of the epidermal growth factor receptor (EGFR) in hepatocytes, which was previously used to infer a strong negative cooperativity between phosphorylation of the adaptor protein Shc and its binding to phosphorylated EGFR. We find that positive cooperativity between the binding of Shc and another adaptor protein, Grb2, to phospho-EGFR can also account for the observed kinetics, and we are currently applying model selection procedures to determine whether one of these mechanisms is favored by the data.

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Why use a modeling language: a view from optimization

Michael C. Ferris

Computer Sciences Department and Wisconsin Institute for Discovery at the University of Wisconsin-Madison, Madison, WI 53706

Abstract

While optimization is prevalent in many application areas, the use of modeling systems such as GAMS and AMPL have until recently been somewhat limited.

We discuss what these modeling languages provide, how to use them in simple cases, what they lack, and a view on their architecture and possible extensions. Several examples will be given, along with some suggestions for design considerations in developing new languages or features, particularly with reference to problems in evolutionary systems biology.

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Evolutionary Dynamics in High Dimensions

Daniel S. Fisher

Applied Physics and Bioengineering, Stanford University

Abstract

Microbial evolution experiments show that there are large numbers of different genes and pathways in which beneficial mutations occur, even in simple environments to which the microbes are already well adapted. The resulting phenotypic changes chemically modify the environment and this can drive further evolution, including coexisting strains rapidly diverging from a clonal ancestor. Almost all genetic changes will have both positive and negative effects, with the balance between these dependent on the environment and the genetic background. And the environmental changes induced by the evolution will have differential effects on fitness that are also composed of both positive and negative parts.
Out of these complexities, one can hope that the very large dimensions of the phenotypic and environmental spaces, the even larger dimensions of the space of protein-level properties --- the huge redundancy that enables evolution --- and the randomness caused by sums of negative and positive effects, might lead to some simplifications. Potential for development and analysis of simple models that caricature some of these complexities will be discussed, with emphasis on open questions and future directions.

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Multidimensional fitness landscapes in evolutionary biology

S. Gavrilets

University of Tennessee

Abstract

The theoretical notion of fitness landscapes (also known as “adaptive landscapes,” “adaptive topographies,” and “surfaces of selective value”), which emerged at the onset of the Modern Evolutionary Synthesis in the 1930s-1940s, has become a standard tool both for formal mathematical modeling and for the intuitive metaphorical visualizing of biological evolution, adaptation, and speciation. I will discuss some recently discovered properties of multidimensional fitness landscapes that are not captured by classical theories (which focused on analogies with geographic landscapes).

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Using high-dimensional yeast-cell phenotyping to screen for polymorphisms influencing trait variability

Kerry A Geiler-Samerotte *& Mark L Siegal*

Center for Genomics and Systems Biology, Department of Biology, New York University

Abstract

Identifying which genetic variants contribute to complex phenotypes and disease is a major goal of modern biology. Screens for such variants are no longer limited to single traits. Instead, an increasing number of studies survey hundreds to thousands of phenotypes at once. Often these phenotypes are not independent, yet very few high-dimensional screens have addressed this issue; most report results assuming independence among phenotypes. We encounter this problem while performing high-dimensional phenotyping to search for polymorphisms that influence trait variability, which are not often studied despite their demonstrable fitness effects. Increased trait variability can be beneficial, for example, microorganisms with increased growth heterogeneity stand a better chance to survive antibiotics. On the other hand, phenotypic variability can be highly undesirable and even buffered during development. Although countless screens have identified polymorphisms that alter the mean values of traits, only a few studies have identified polymorphisms that alter trait variances. Because the prevalence of polymorphisms that influence variability is unknown, we utilize high-dimensional phenotyping to assay many traits for genetic effects on variability. We measure 200 morphological parameters in 374 segregating yeast strains from a cross between morphologically divergent parents. Using strict statistical cutoffs, we identity 20 genetic regions that contribute to the average morphology of each strain, but we detect none that independently influence morphological variability of each strain. The apparent rarity of polymorphisms influencing variability may be less striking given the 200 phenotypes we measure are partially redundant; for example, cell size correlates strongly with cell width. Correlation between phenotypes poses other problems for our study as well. For example, redundant phenotypes introduce bias when we ask what fraction of overall morphological diversity is heritable. An exploration of various techniques to reduce redundancies (*e.g.* principal component analysis, partitioning around medoids, GFLasso) presents several solutions, but none are yet ideal for our purposes. Methods that simultaneously model means and variances of multiple, potentially correlated traits are needed to understand how genetic variation shapes the phenotypes we observe in nature.

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The adaptive origin of epigenetic switches in fluctuating environments

Mariana Gomez-Schiavon[1] *& Nicolas Buchler*[2]

[1]*Computational Biology and Bioinformatics, PhD program, Duke University*
[2]*Duke Center for Systems Biology; Physics and Biology Department; Duke University*

Abstract

How organisms adapt and survive in continuously fluctuating environments is a central question of evolutionary biology. Epigenetic switches have been suggested as one mechanism of bet-hedging and adaptation to fluctuating environments (Jablonka *et al.*, 1992). An epigenetic switch is a system capable of switching between two or more stable phenotypes, where the phenotype is inherited through multiple generations with no underlying DNA mutation; this requires an initiating event, which can depend on some external input or it may be induced by stochastic fluctuations (Iliopoulos *et al.*, 2009). The extent to which epigenetic switches emerge as an adaptation to fluctuating environments remains unknown.

Here, we use computer simulation to evolve a large population of cells containing an auto-regulatory gene, the simplest molecular system capable of displaying stochastic epigenetic switching (bistability). Our goal is to use this mechanistic model (which includes intrinsic biochemical noise) to understand the specific evolutionary conditions that lead to the selection of bistability under a fluctuating environment. This *in silico* laboratory allows us to run many experiments to uncover any statistical regularities of evolution. Our preliminary results show that gradually decreasing the genetic adaptation time (*e.g.* by increasing the mutation rate) changes the selected strategy from epigenetic switching to genetic adaptation for a range of environmental fluctuation frequencies. Based on the insights obtained from *in silico* evolution, our eventual goal is to test the adaptive origin of epigenetic switches using laboratory evolution of an auto-regulatory gene circuit.

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Protein Domains with Greater Influence on Network Dynamics Evolve More Slowly

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Abstract

A fundamental question for evolutionary biology is why different proteins evolve at dramatically different rates. In particular, it is controversial to what degree the functional importance of a protein affects its evolutionary rate, in part because functional importance can typically only be experimentally measured crudely, using knock-outs. Here we leverage biochemically-detailed systems biology simulation models to measure importance much more finely. We define the dynamical influence of a protein domain as the integrated sensitivity of network dynamics to changes in the rate constants of reactions that domain participates in. We show that protein domains with greater dynamical influence typically evolve more slowly, in both vertebrates and yeast, suggesting that functional importance does indeed affect protein evolutionary rate. We also show that dynamical influence and knock-out essentiality are not strongly correlated, suggesting that many cellular reactions are essential to life but have little quantitative effect on fitness.

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Stickbreaking: A Novel Fitness Landscape Model That Harbors Epistasis and Is Consistent with Commonly Observed Patterns of Adaptive Evolution

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Abstract

In relating genotypes to fitness, models of adaptation need to both be computationally tractable and qualitatively match observed data. One reason that tractability is not a trivial problem comes from a combinatoric problem whereby no matter in what order a set of mutations occurs, it must yield the same fitness. We refer to this as the bookkeeping problem. Because of their commutative property, the simple additive and multiplicative models naturally solve the bookkeeping problem. However, the fitness trajectories and epistatic patterns they predict are inconsistent with the patterns commonly observed in experimental evolution. This motivates us to propose a new and equally simple model that we call stickbreaking. Under the stickbreaking model, the intrinsic fitness effects of mutations scale by the distance of the current background to a hypothesized boundary. We use simulations and theoretical analyses to explore the basic properties of the stickbreaking model such as fitness trajectories, the distribution of fitness achieved, and epistasis. Stickbreaking is compared to the additive and multiplicative models. We conclude that the stickbreaking model is qualitatively consistent with several commonly observed patterns of adaptive evolution.

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Universality in the evolution of molecular quantitative traits

Torsten Held (1), Armita Nourmohammad (2), Stephan Schiffels (1,3),
Michael Laessig

(1) University of Cologne
(2) Princeton University
(3) Sanger Institute, UK

Abstract

Molecular phenotypes are important links between genomic information and organismic functions that contribute to fitness and evolution. Quantitative traits, such as gene expression levels, depend on multiple genomic loci. Their sequence evolution is a complicated process that involves selection, genetic drift, mutations, and recombination. At the phenotypic level, however, quantitative traits have a ``universal'' evolutionary statistics, which decouples from details of their genetic basis. In particular, we derive and apply a universal method to infer basic modes of trait evolution: conservation and adaptive change. We discuss the implications of our findings for the predictability of evolutionary processes.

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Co-evolution and mutation-selection balance in the evolution of metabolic pathways

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Abstract

Using simulations, the co-evolution of Kcat and Km in metabolic pathways is evaluated over 5 network topologies, a range of mutation rates (including duplication and loss rates), population sizes, and selective regimes using a kinetic model. The pathways are model versions of glycolysis, steroid/carotenoid biosynthesis, the citric acid cycle, arachidonic acid metabolism, and dihydroxyacetone phosphate metabolism. Biochemical thought is that there is strong selective pressure to preserve rate limiting steps at early steps in pathways to prevent wasteful protein expression and to prevent the buildup of potentially deleterious intermediates in large concentrations. Evolutionary thought is that mutation-selection balance is an important aspect of the evolutionary dynamics of pathways, leading to evolutionary instability of rate limiting steps when selection is weak or effective population size is small. These dynamics are examined under selective regimes that also include either negative or positive selective pressures on pathway flows and outputs.

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Evolutionary Systems Biology, Fitness Landscapes and Evolvix

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Laboratory of Genetics and Wisconsin Institute for Discovery at the University of Wisconsin-Madison

Definition

Evolutionary systems biology aims to ultimately build realistic integrated simulators for fitness landscapes that mechanistically predict observable
(i) fitness changes from changes in genotype and environment, as well as
(ii) evolutionary paths for real populations.

Some longstanding questions in evolutionary biology and population genetics could be answered if we had an appropriate understanding of the effects of mutations on an organism. Evolutionary biologists have quantified these effects using selection coefficients and various measures of epistasis that describe interactions between different mutations, resulting in simplistic overviews.

While appropriate for some topics, many questions in evolutionary biology require a more mechanistic understanding. Such a deeper understanding could come from computational models that are being constructed in molecular systems biology. These models encapsulate many mechanistic details from careful observations and often represent the state of the art of our knowledge of the corresponding biological systems. Such models allow for 'mutagenesis' on a new level by enabling automated evaluations of many *in silico* mutations by simulation. To the degree that such simulations can compute fitness correlates, they bring us closer to a more mechanistic understanding of fitness landscapes.

To this end we need to evaluate many diverse models, making construction and analysis of realistic systems biology models an important bottleneck. This motivates the design of Evolvix, a new model description language that we build to make model description as simple as possible for biologists (enabling them to build more models). We aim to provide automated evaluations of fitness landscapes for models described in Evolvix and thus enable a broader and more realistic view of the fitness landscapes that shape the evolution of life in the real world.

In this talk I will explain this view of evolutionary systems biology and illustrate core principles of the corresponding analyses using a simple circadian clock model. While Evolvix is still under construction (see Evolvix.org), I will give a brief outline of plans in order to invite input and feedback from the community. It is our goal to build a software ecosystem around Evolvix that makes it easy to include new simulators and new analyses to make Evolvix as useful as possible for a community that is as broad as feasible. We hope this will facilitate a deeper understanding of fitness landscapes and evolution in natural populations.

Loewe (2009) A framework for evolutionary systems biology *BMC Syst. Biol*. 3:27

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Robustness and evolvability

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Abstract

Robustness and evolvability are two quintessentially systems properties for which a formal evolutionary perspective is essential. The relationship between robustness and evolvability is discussed using two quite different metaphors and hence classes of model (Trotter & Masel 2010). In recombining populations, robustness allows the accumulation of cryptic genetic variants, whose phenotypic effects may first become apparent under decanalizing stress, and later become genetically assimilated after recombination brings polygenic allele frequencies above a threshold. When recombination can be ignored, whether for single genes or whole asexual systems, then populations can instead be visualized in a high-dimensional space, where each node is a genotype and edges represent mutations between them. Evolvability always depends on the quantity and quality of available heritable phenotypic variants. In genotype space, quantity arguments focus on robustness allowing a population to “spread” across more nodes, and access more future genotypes via new mutations. Quality arguments demonstrate evolution not towards nodes of higher mutational “neighborhood richness”. For example, present errors in transcription, splicing, translation, folding and/or binding can mimic future mutations (Rajon & Masel 2011). This allows selection to preview the phenotypes of neighboring genotypes, even before those genotypes appear by mutation. We find that for polygenic traits, neighborhood richness, rather than population spread, is responsible for high evolvability (Rajon & Masel 2013).

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Building fitness landscapes based on models of well-characterized biological systems

Maria Safi, Ryan Lilen and ***Alan M Moses***

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Abstract

Fitness Landscapes have long been discussed in evolutionary biology, and although they have proven conceptually useful, the complexity of the relationship between genotype and phenotype in general has prevented the construction of such landscapes for real biological systems. By taking advantage of abundant computing power, recent advances in modeling appraoches and the detailed molecular information that is available for some well-characterized systems, we are attempting to get a first look at some actual fitness landscapes. We have used force-field calculations and simple assumptions about the relationship between binding energy and fitness to build fitness landscapes for the HIV protease under selective pressure from various inhibitors. With a few approximations, we can simulate evolution on these landscapes, and find reasonable agreement between our simulations and observed evolution of drug resistance in patients. Our approach should be applicable to any system for which a quantitative connection between genotype and fitness can be made based on a computational or mathematical model. While it does give a first look at evolutionary dynamics on a “real” fitness landscape, I will also point out several remaining challenges where our approach could be improved.

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Genotype to phenotype mapping and the fitness landscape of the E. coli lac promoter

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Abstract

Genotype-to-phenotype maps and the related fitness landscapes that include epistatic interactions are difficult to measure because of their high dimensional structure. Recently we constructed such a map using high-throughput sequence data from the 75 base pairs long mutagenized *E. coli* lac promoter region, where each sequence is associated with its phenotype, the induced transcriptional activity measured by a fluorescent reporter. We found that the additive (non-epistatic) contributions of individual mutations accounted for about two-thirds of the explainable phenotype variance, while pairwise epistasis explained about 7% of the variance for the full mutagenized sequence and about 15% for the subsequence associated with protein binding sites. Surprisingly, there was no evidence for third order epistatic contributions, and our inferred fitness landscape was essentially single peaked, with a small amount of antagonistic epistasis. We found a significant selective pressure on the wild type, which we deduced to be multi-objective optimal for gene expression in environments with different nutrient sources.

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Stochastic Simulation Service: Towards an Integrated Development Environment for Modeling and Simulation of Biological Processes

***Linda Petzold**, Chandra Krintz, Andreas Hellander*

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Abstract

In recent years it has become increasingly clear that stochasticity plays an important role in many biological processes. Examples include bistable genetic switches, noise enhanced robustness of oscillations, and fluctuation enhanced sensitivity or “stochastic focusing". In many cellular systems, local low species populations can create stochastic effects even if total cellular levels are high. Numerous cellular systems, including development, polarization and chemotaxis, rely on spatial stochastic noise for robust performance. In this talk we report on our progress in developing next-generation algorithms and software for modeling and simulation of stochastic biochemical systems, and in building an integrated development environment that will enable researchers to build a such a model and scale it up to increasing levels of complexity.

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Sex and Arithmetic in Nematodes

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Abstract

Over the last decade, gene expression has been a common focus of evolutionary systems biology. New techniques for measuring mRNA levels in single cells have revealed that inter-individual variation in gene expression can be extensive, even between genetically identical organisms, suggesting that stochasticity during development may play an important role in generating phenotypic variation. However, in other cases, cells make reliable and consistent fate decisions even in the face of molecular diversity. This highly resolved, quantitative, and often dynamic data could be a fruitful intersection of theoretical and experimental evolutionary systems biology. In this talk, I will discuss a system where an organism uses somewhat noisy gene expression to make a precise and evolutionarily crucial developmental decision.

Although the sex of an organism is commonly encoded genetically, sex determination is a developmental process. The encoded information must be read, interpreted, and acted upon. Caenorhabditis elegans has chromosomal sex determination where worms with two X chromosomes become hermaphrodites and the rare worm with only one X chromosome becomes male. Worms precisely measure the ratio of X chromosomes to autosomes by a game of molecular tug-of-war. Regulators on the X chromosomes try to repress the key gene xol-1 while regulators on the autosomes try to activate it. The competition takes place largely at the xol-1 promoter and is focused on transcription. I will discuss three questions about C. elegans sex determination using in situ measurements of gene expression with single molecule spatial resolution: (1) When does a worm decide what sex it is? (2) Does each cell make this decision on its own? (3) What are the dynamics of the regulatory tug-of-war?

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Phenotypic Deconstruction Of Biochemical Systems

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Abstract

Although we now have a generic concept of 'genotype' provided by the detailed DNA sequence of an organism, there is no corresponding concept of 'phenotype'. The concept of phenotype must ultimately be grounded in the underlying biochemistry. Achieving predictive understanding of complex nonlinear systems, such as those manifested at various levels of biological organization, is at the heart of the 'Genotype to Phenotype Problem' and represents an enormous challenge. The task could be facilitated if such systems could be deconstructed into a set of tractable nonlinear sub-systems and the results of their analysis reassembled to provide insight into the original system. The system design space methodology, which addresses this issue, provides two innovations that show promise for dealing with the genotype-phenotype challenge. First, it provides a mathematically rigorous definition of *phenotype* as a combination of dominant processes having boundary conditions within which the phenotype is valid. Second, it provides for the *deconstruction of complex systems* into a finite number of mathematically tractable nonlinear sub-systems representing qualitatively distinct phenotypes. This deconstruction based on phenotypic differences differs from the traditional approaches to deconstruction based on differences in space, time or function. This method efficiently characterizes large regions of system design space and quickly generates alternative hypotheses for experimental testing. It provides a means of graphically illuminating the relationship between genetically-determined parameters, environmentally-determined variables, and the qualitatively distinct phenotypes of the system.

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Nonlinearity, Evolvability and Robustness in Gene Regulation Networks

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Abstract

The description of biological systems in the context of evolution often involves statements on their evolvability and robustness. The relationship between these two properties could be expressed in form of a paradox: how can biological systems be robust to mutations and at the same time allow for innovation? At a molecular level, we expect such features to reflect dynamic properties of a system of interest, such as of metabolic or gene regulation networks. In recent years there have been several attempts to quantify robustness and evolvability at subcellular scales, as well as relating these measures to each other and thereby resolving the paradox stated above. In our study, we extend such approaches by also incorporating dynamical informations usually gained from a systems biology approach, such as stability and ultrasensitivity. In doing so, we are able to elucidate on the mechanistic underpinnings of the robustness-evolvability paradox.
We investigated the genotype-phenotype map of an auto-regulating feedback circuit. As a result, the relationship between robustness and evolvability of gene expression levels could be studied in great detail. Different mathematical quantification methods of both measures were developed and compared to each other. Specifically, we eluded on the role of nonlinearity in the relationship between robustness and evolvability. By extending this analysis to other typical motifs in gene regulation, we are able to draw more general conclusions about this relationship.

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Identifying the sources of variation in biochemical networks

Clive Bowsher, Margaritis Voliotis & ***Peter Swain***

University of Edinburgh

Abstract

To understand how cells control and exploit biochemical fluctuations, we must identify the sources of stochasticity, quantify their effects, and distinguish informative variation from confounding "noise". I will present an analysis that allows fluctuations of biochemical networks to be decomposed into multiple components and will identify a particular component that quantifies the efficacy of information flow through a biochemical network. Using these ideas, I will present a general methodology for analyzing the fidelity with which different statistics of a fluctuating input are encoded in the output of a signaling system over time.

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Optimal and mechanistic solutions for the expression of age-dependent plasticity

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Abstract

When organisms encounter environments that are heterogeneous in time, phenotypic plasticity is often favored by selection. The degree of such plasticity can vary during an organism's lifetime, but the factors promoting differential plastic responses at different ages or life stages remain poorly understood. I will first introduce a constraint-free evolutionary model, which assumes that individuals are capable of Bayesian updating, and investigate how environmental information is optimally collected and translated into phenotypic adjustments at different ages. This model indicates that plasticity must often be expected to vary with age in a non-monotonic fashion. Next, I develop mechanistic models of protein-interaction networks, and study to what extent these are capable of implementing the predicted optimal reaction norm for age-dependent plasticity. The results from both models clarify how patterns of age-dependent plasticity are shaped by environmental uncertainty, the accuracy of perceived information, life-history determinants and developmental constraints.

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Evolution of expression noise in native and synthetic *E. coli* promoters

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Abstract

It is well appreciated that, due to the intrinsically stochastic nature of the mechanisms involved in gene expression, genetically identical bacterial cells in identical environments show significant fluctuations in gene expression levels, i.e. `expression noise'. Since optimal growth depends on gene products being expressed at appropriate relative levels, it is may be expected that natural selection has acted to minimize gene expression noise.
To investigate the selection on expression noise that natural promoters have experienced, we compared noise characteristics of native *E. coli* promoters with those of synthetic promoters, evolved in the lab from entirely random sequences under conditions in which noise is not under selection. Surprisingly, we find that native promoters generally show *higher* levels of noise than synthetic promoters. I will discuss these results in the context of a number of simple theoretical evolutionary models and considerations and will argue that selection for expression noise is to be expected whenever regulatory systems are imprecise.

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Mobile Promoters: A new addition to the mobilome?

Lindi Wahl, *Mariana Matus-Garcia, Harm Nijveen, Mark van Passel*

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Abstract

Recent studies of prokaryotic genomes have identified promoter sequences which appear to be mobile genetic elements. These "putative mobile promoters" (PMPs) are identified by finding homologous promoter sequences that are associated with non-homologous coding sequences. We have extended this dataset to identify the full complement of mobile promoters in sequenced prokaryotic genomes, finding over 40,000 homologous promoter sequences. To gain further insight, we developed a birth-death-diversification model for mobile genetic elements subject to sequence diversification; applying the model to PMPs we were able to quantify the relative importance of duplication, loss, horizontal gene transfer (HGT) and diversification to the maintenance of the PMP reservoir. We also use a toy model of a regulatory network to investigate the possible phenotypic effects of promoter mobilization.

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"Convergent evolution of hyperswarming in experimental bacterial populations"

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Abstract

The opportunistic pathogen Pseudomonas aeruginosa forms biofilms in cystic fibrosis lungs that are notoriously difficult to treat with antibiotics. Alternative approaches are desperately needed to fight these biofilm infections. One possibility lies in the inverse genetic regulation of motility and biofilm formation of P. aeruginosa. We investigated whether pushing the bacterium to a motile state makes it form less biofilm. In evolutionary experiments we applied a selective pressure for swarming, a collective form of motility where colonies of P. aeruginosa form striking branched patterns on soft surfaces. The experiments consistently produced P. aeruginosa mutants that went from being mono-flagellated, their natural state, to become multi-flagellated, which made them swim faster and out-compete the ancestral strain. The advantage in swarming came with a trade-off: multi-flagellated mutants do not compete well in biofilm communities, which would be essential for their survival in environmental and clinical settings. The observation that selection for superior motility consistently leads to the evolution of weak biofilm formers could open new therapeutic avenues against persistent biofilm infections.

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Developmental cell lineages are robust to cell death

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Abstract

Phenotypic robustness of organisms to environmental and genetic perturbations is an important characteristic of life. Although development has long been thought to be a key component of phenotypic robustness, the underlying mechanism is poorly understood. Here we report that developmental cell lineages of two protostome and one deuterostome animals are structured such that the resulting cellular compositions of the organisms are only modestly affected by cell deaths due to random necrosis and cell division program failure, which respectively represent environmental (or somatic) and genetic (i.e., germline) disturbances. Several features of the cell lineages, including their shallowness, topology, early ontological appearances of rare cells, and non-clonality of most cell types, underlie the robustness. Evolutionary simulations show that cell lineage robustness can arise as an adaptation to environmental but not genetic perturbations. These results reveal general organizing principles of developmental cell lineages and a conceptually new mechanism of phenotypic robustness, both of which have important implications for development and evolution.