1st mini symposium series on Stochasticity and Control in Biological Systems

Date	Time and Speaker	Title	Type
Tuesday 28.3.2017	12:00 Avigdor Eldar	Eco-evolutionary dynamics of microbial communication - me, us and them	Open seminar
	14:00 Nadav Kashtan	Bacterial decision making on unsaturated surfaces	
Tuesday 4.4.2017	12:00 Yoni Savir	Yeast response to multiple carbon sources: a case study of combinatorial signal integration	Open seminar
	14:00 Naama Barkai	How 'noise' can help microorganisms adapt to fluctuating environment?	
Wednesday 19.4.2017	12:00 Ruti Hershberg	From boom to bust - the dynamics of bacterial adaptation under prolonged resource exhaustion.	Open seminar
	14:00 Omry Koren	We are not alone: a meeting with your gut microbiome	
Tuesday 25.4.2017	12:00 Benny Chain	The T cell receptor repertoire in lung cancer	Open seminar
	14:00 Itzhak Haviv	Using technology to negotiate genotype-phenotype interface in health and disease	
Wednesday 3.5.2017	12:00 Michael Assaf	Aspects of stochastic population dynamics in gene expression and cellular decision making	Open seminar
	14:00 Uri Nevo	Ecology resolves the complexity of immune self-tolerance	
Tuesday 9.5.2017	12:00 Erez Braun	Cell-state organization: The living cell as a sloppy dynamical system	Open seminar
	14:00 Leila Perie	Deciphering the family tree of immune and blood cells	
Tuesday 16.5.2017	12:00 Mickey Kosloff	Deciphering the structural design principles for interaction specificity among signaling proteins	Open seminar
	14:00 Eran Meshorer	Epigenetics and expression heterogeneity in mouse embryonic stem cells	
Monday 29.5.2017	12:00 Tomer Kalisky	Cellular heterogeneity in kidney tissues and tumors	Open seminar
	14:00 Naama Brenner	Exploratory adaptation in gene regulatory networks	
Tuesday 6.6.2017	12:00 Tamir Tuller	Building Models for Understanding and Engineering Gene Expression Dynamics	Open seminar
Tuesday 13.6.2017	12:00 Tal Shay	Challenges in extracting splicing preference from single RNA-sequencing data	Open seminar
	14:00 Martin Flajnik	The origins of cellular selection in adaptive immunity	

Tuesday 27.6.2017	12:00 Sarel Fleishman	Learning from antibodies how to design new protein functions	Open seminar
	14:00 Adi Stern	Viral evolution: living on the edge	
Wednesday 28.6.2017	11:00 Bartlomiej Swiatczak	Immune balance: Towards a dynamic view of immune behavior	Open seminar

Eco-evolutionary dynamics of microbial communication - me, us and them

Avigdor Eldar (Tel Aviv University)

Bacteria use simple cell-cell communication systems to monitor their density in the environment and control collective behaviors. This quorum-sensing mechanism works by the secretion of a small diffusible molecule and its identification by a specific receptor. Many bacterial species show divergence in their quorum-sensing "languages", reflected in the co-expression of multiple quorum-sensing systems and in high levels of genetic variability within the population. Here I explore the impact of cell-cell signaling on sociality at three different levels, using Bacillus subtilis as a model system. At the physiological level, I show that different types of quorum-sensing systems show 'self-sensing' – i.e., respond cell-autonomously to their own signal. At the ecological level, I show that exploitive social selection can explain the observed diversity patterns of different types of quorum-sensing systems. Finally, at the evolutionary level, we find that lateral gene transfer and gene duplication contribute to the evolution of quorum-sensing diversity at different levels of genomic organization.

Related Research Questions

1) **The problem of evo-devo in bacteria:** What is the interplay between regulatory network structure and selection?

2) **Social evolution in bacteria:** Does social evolution drives bacterial diversification?

3) **Bacterial cell-cell signaling:** How does diversity in bacterial cell-cell signaling systems arise and what are its impacts on their function?

Suggested Reading

Facultative cheating supports the co-existence of multiple quorum-sensing pherotypes.
Shaul Pollak, Shira Omer Bendori, Eran Even-Tov, Valeria Lipsman, Tasneem Bareia, Ishay Ben-Zion,Avigdor Eldar
PNAS, 113(8):2152-7 (2016)

Social evolution selects for redundancy in bacterial quorum sensing.
Eran Even-Tov, Shira Omer Bendori, Julie Valastyan, Xiaobo Ke, Shaul Pollak, Tasneem Bareia, Ishay Ben-Zion, Bonnie L. Bassler and Avigdor Eldar
PLoS Biology, 14(2): e1002386 (2016)

Transient Duplication-Dependent Divergence and Horizontal Transfer Underlie the Evolutionary Dynamics of Bacterial Cell–Cell Signaling
Eran Even-Tov, Shira Omer Bendori, Shaul Pollak, Avigdor Eldar
PLoS Biology, 14(12): e2000330 (2016)

Bacterial Decision Making on Unsaturated Surfaces

Nadav Kashtan (The Hebrew University)

Bacteria respond and adapt to their environment by various means, one of the most apparent is the choice between surface-attached biofilm and solitary planktonic lifestyles. These distinct states impose tradeoffs between growth and survival which affect the fitness of individual cells under different conditions. Here, we ask how and to what extent an information-based decision to change states can improve bacterial fitness in fluctuating hydration conditions. To study this question, we use the phyllosphere – the above-ground parts of plants – as a model system. The phyllosphere is a huge microbial habitat dominated by leaf surfaces, where bacterial cells are observed either as solitary cells or within aggregates. These bacteria confront significant diel changes in hydration conditions (wet nights and dry days). We use an individual-based model to simulate bacterial colonization of a leaf surface. Simulated bacterial cells may attach or detach to/from the surface, switching between planktonic and biofilm states. The motile planktonic bacteria grow faster but have lower survival rates during dry periods. In contrast, bacteria in large aggregates grow slower, but gain a higher resistance to desiccation. In our model, attachment of a cell to the surface can occur either stochastically or by a simple preferential attachment strategy, cued by quorum-sensing signals, which provide information about the local density of bacteria on the surface at the microscale. We demonstrate that at conditions typical to the leaf surface the preferential attachment strategy carries a large fitness advantage over any stochastic strategy. The emergent collective ability to regulate the dynamics of the aggregate-size distribution, which arises from the individual behavior of cells, proves critical at the early colonization stages. We argue that the resulting partition of planktonic and biofilm states and the dynamics of spatial organization can be conceptualized as resource allocation optimization.

Related Research Questions

1. Can we predict the spatial organization and dynamics of complex surface-related bacterial communities?

2. How does single-cell behavior control emergent collective properties of bacterial populations?

3. What is the selective advantage of given individual bacterial behaviors that control collective properties of the population?

Suggested Reading

Microbiology of the phyllosphere: a playground for testing ecological concepts.
Meyer KM, Leveau JH
Oecologia, 168: 621 (2012)

Differential survival of solitary and aggregated bacterial cells promotes aggregate formation on leaf surfaces
J.-M. Monier and S. E. Lindow
PNAS, 100 (26) 15977-15982 (2003)

The sociobiology of biofilms
Nadell CD, Xavier JB, Foster KR.
FEMS Microbiol Rev, 33 (1): 206-224 (2009)

Phenotypic diversity, population growth, and information in fluctuating environments.
Kussell E, Leibler S.
Science, 309 (5743), 2075-2078 (2005)

Yeast response to multiple carbon sources: a case study of combinatorial signal integration

Yoni Savir (Technion)

A major determinant of the fitness of biological systems is their ability to integrate multiple cues from the environment and coordinate their metabolism and regulatory networks accordingly. While much is known about the response to a single stimulus, our understating of combinatorial integration of multiple inputs is still limited. As a model system, we studied how yeast responds to hundreds of mixtures of preferred carbon source, glucose, and a less preferred one, galactose. Many of the components of this response, known as catabolite repression, are conserved from yeast to human. We found that, in contrast to the textbook view, instead of simply inhibiting galactose utilization when glucose is above a threshold concentration, individual cells respond to the ratio of glucose and galactose, and based on this ratio determine whether to induce genes involved in galactose metabolism. We investigate the genetic architectures that can result in a ratio sensing and how these architectures provide a fitness advantage which could have shaped the evolution of this property.

Related Research Questions

1. How does combinatorial nutrient sensing change as the cells age? Can we reverse nutrient sensing failure?
2. What types of biological circuits allow coping with high-dimensional input space?
3. What (if any) are the optimal switching strategies when a system changes its output behaviors based on multiple inputs? For instance when cells change metabolic gene programs in the presence of preferred and less preferred resources.

Suggested Reading

Achieving global perfect homeostasis through transporter regulation (2017)
Savir, Y., Martynov,A, Springer M.
Plos Comp Bio

Competitive Inhibition Can Linearize Dose-Response and Generate a Linear Rectifier (2015)
Savir, Y., Tu, BP, Springer, M.
Cell Systems

Galactose metabolic genes in yeast respond to a ratio of galactose and glucose (2015)
Escalante R.*, Savir, Y.*, Carroll, SM., Ingraham, J.B., Wang, J., Marx, C.J., and Springer, M.
Proc Natl Acad Sci USA 112(5): 1636-1641.

How ‘noise’ can help microorganisms adapt to fluctuating environment?

Naama Barkai (Weizmann)

Cells process information using circuits of interacting genes and proteins. Reliable performance of these circuits is often challenged by biological variability. Such variability results from genetic polymorphism, changes in the environment, or to random noise. We investigate the possible effects of this variability on the design of biological circuits. I will describe several of our studies, where we find that noise enables improved designs, not possible by a fully deterministic dynamics.

Related Research Questions

1. How do cells adapt to fluctuating environment?
2. Can ‘noise’ benefit cells’ growth and survival?
3. Can cells control the rate of genetic mutations, and does ‘noise’ play a role in this process?

Suggested Reading

Coupling phenotypic persistence to DNA damage increases genetic diversity in severe stress;
Gilad Yaakov*‡ , David Lerner‡ , Kajetan Bentele†‡, Joseph Steinberger† and Naama Barkai*
Nature Ecology and Evolution, Volume 1, January 2017

Increasing population growth by asymmetric segregation of a limiting resource during cell division.
Avraham N, Soifer I, Carmi M, Barkai N.
Mol Syst Biol.2013 Apr 16;9:656. doi: 10.1038/msb.2013.13.

Budding yeast escape commitment to the phosphate starvation program using gene expression noise.
Vardi N, Levy S, Assaf M, Carmi M, Barkai N.
Curr Biol. 2013 Oct 21;23(20):2051-7. doi: 10.1016/j.cub.2013.08.043

The competitive advantage of a dual-transporter system.
Levy S, Kafri M, Carmi M, Barkai N.
Science. 2011 Dec 9;334(6061):1408-12. doi: 10.1126/science.1207154.

From boom to bust - the dynamics of bacterial adaptation under prolonged resource exhaustion

Ruti Hershberg (Technion)

Many bacteria, including the model bacterium *Escherichia coli* can survive for years within spent media, following resource exhaustion. We carried out evolutionary experiments, followed by full genome sequencing of hundreds of evolved clones to study the dynamics by which *E. coli* adapts during the first four months of survival under resource exhaustion. Our results reveal that bacteria evolving under resource exhaustion are subject to intense selection, manifesting in rapid mutation accumulation, enrichment in functional mutation categories and extremely convergent adaptation. Our results further demonstrate that such adaptation is not limited by mutational input. Indeed, mutational input appears to be high enough to enable bacteria to rapidly adapt, in a highly convergent manner and with great temporal precision through fluctuations in allele frequencies. Finally, we demonstrate that due to antagonistic pleiotropy and mutation accumulation, survival under resource exhaustion can severely reduce a bacterium's ability to grow exponentially, once resources are again available. Combined, our results shed light on bacterial adaptation to long-periods of resource exhaustion and on the consequences such adaptation has on the genetic makeup of individual bacteria and on patterns of genetic variation within bacterial populations.

Related Research Questions

General question:

1. How do bacteria adapt to survive under prolonged resource exhaustion and with what consequences on individual bacteria and on the entire bacterial population?

Specific questions:

1. To what extent does survival under resource exhaustion require genetic adaptation?
2. Is adaptation under resource exhaustion limited by mutation input?
3. Does adaptation to resource exhaustion incur a cost on later growth, when resources are again available?

Suggested Reading

Rapid genetic adaptation during the first four months of survival under resource exhaustion.
Sarit Avrani, Evgeni Bolotin, Sophia Katz and Ruth Hershberg, (in press 2017).
Molecular Biology and Evolution

We are not alone: a meeting with your gut microbiome

Omry Koren (BIU)

The gut microbiome is the collection of microorganisms including bacteria, archaea, viruses and fungi found within the gut and their genetic information. Our gut microbiota has been shown to have broad effects on our health and well-being, impacting our immune system and metabolism, detoxifying various ingested components, and even effecting behavior. Changes in gut microbiota composition are correlated with different life stages, diet and geographical location, exercise, use of antibiotics and a wide range of disease states. In the next years, this rapidly growing research field is likely to provide more precise interactions and networks connecting hosts with their microbiome.

Related Research Questions

1. How is the microbiota assembled and maintained over a lifetime?
2. How personal is each individual's microbiota?
3. How does its composition contribute to well-being or disease predisposition and pathogenesis?

Suggested Reading

Structure, function and diversity of the healthy human microbiome.
Human Microbiome Project C
Nature 2012, 486(7402):207-214.

Unravelling the effects of the environment and host genotype on the gut microbiome
Spor A, Koren O, Ley R
Nat Rev Microbiol 2011, 9(4):279-290.

Conducting a microbiome study
Goodrich JK, Di Rienzi SC, Poole AC, Koren O, Walters WA, Caporaso JG, Knight R, Ley RE.
Cell 2014, 158(2):250-262.

Interpreting the T cell receptor repertoire

Benny Chain (UCL)

The T cell repertoire consists of an ensemble of alpha and beta T cell receptor (TCR) sequences which characterize a blood or tissue sample at a particular time. We understand in detail the molecular interaction between an individual T cell receptor and its cognate peptide/MHC antigen target, but the impact of antigen exposure on the repertoire as a whole is less well understood. The problem is compounded because the stochastic nature of TCR generation results in different repertoires between individuals. We approach the problem from the perspective of classification of repertoires after immunisation with different antigens in a space indexed by all possible TCRs (we focus on CDR3 sequences, which play a major role in antigen recognition). We reduce dimensionality by decomposing each CDR3 into sets of short amino acid motifs. From a biophysical perspective, these motifs may capture conserved contact points between TCR and MHC/peptide complex. The frequency of each motif in a sample of TCRs after immunisation with a given antigen defines the repertoire in a new feature space. We use support vector machines and other weak learner algorithms to identify set of features which correctly classify repertoires from different immunisations. The results suggest that immunisation induces widespread changes in the TCR repertoire distributed over a large number of individual TCRs. Short amino acid motifs, often situated at the ends of the CDR3 region, confer degenerate antigen specificity in the context of a highly diverse and largely private set of T cell receptors.

Related Research Questions

1. How does the T cell receptor repertoire reflect the antigen specific response?
2. Is T cell receptor recognition dependent on interaction of small linear sequences within the CDR3s?
3. Can the T cell repertoire act as biomarker for infection?

Suggested Reading

n/a

Using technology to negotiate genotype-phenotype interface in health and disease

Izhak Haviv (BIU)

This talk aims to compare hypothesis driven research with high throughput sample profiling. I make an argument that the principal paradigm, responsible for the significant life span increase, offered by medical research, is the Koch postulates. Unfortunately, for some diseases such as cancer, this paradigm failed to provide the same level of cure. Simply knowing that cancer cells grow more, die less, and migrate is just not enough to develop molecules with sufficient therapeutic window to exhibit efficacy. We do know that cancer is a disease of DNA sequence, and had extensively catalogued the cancer genome, and yet, cancer mortality relents. While the abstract principle that cancer cells have altered DNA prevails, the actual sequence changes that occur in each case are so variable, that there is really no two cancer cases that formally are of identical etiology. Therefore, novel and commonly effective drugs only benefit a small fraction of the patients, thus the term “personalized medicine”. Furthermore, while novel cures appear very promising in pre-clinical models, for most cancer therapies, acquired resistance is the common case, and cure simply means delaying the end. This exceptional resilience to cure is shared between cancer and some viral infections, and the common mechanism is evolution. One simple conclusion is that cancer would be easier to prevent than cure. However, two methods have overcome this evolutionary plasticity challenge in the case of viral infectious diseases, and are starting to also impact cancer care. The first is combination therapy, and the second is evoking an immune reaction against the diseased cells. The field of genetics was founded on the attempt to understand outlier phenotypes. However, evidence in different fields of genetics point to the joint effect of both nature as well as nurture, i.e. the character traits of an organism are collectively contributed to by both innate qualities, such as DNA sequence, as well as the individual's personal experiences ("nurture" in the sense of environmental factors of lifestyle or lifetime exposure). We found multiple modes, by which cancer exploits both nature (sequence mutations) as well as nurture (cancer stromal neighboring cells and epigenetics) to derive novel variants that would evade therapy via simple evolutionary principles. The argument is therefore, that widely effective cancer cure would require integration of multiple parallel approaches, as well as significant widening of the way we interpret the cancer genomic information.

Related Research Questions

1. Why do we conduct and support science; for education and professional training, for insight and accumulation of knowledge, or to benefit mankind?
2. If the third answer to the previous question is partially true, how can we make research more effective in delivering benefit?
3. What is the limiting step to more effective cancer cures; funding, knowledge, or paradigm change?

Suggested Reading

Whole-genome characterization of chemoresistant ovarian cancer.
Patch AM et al.
Nature. 2015 Nov 19;527(7578):398.

Mechanisms underlying mutational signatures in human cancers.
Helleday T, Eshtad S, Nik-Zainal S.
Nat Rev Genet. 2014 Sep;15(9):585-98. doi: 10.1038/nrg3729. Epub 2014 Jul 1. Review.

Immunogenicity of somatic mutations in human gastrointestinal cancers.
Tran E, Ahmadzadeh M, Lu YC, Gros A, Turcotte S, Robbins PF, Gartner JJ, Zheng Z, Li YF, Ray S, Wunderlich JR, Somerville RP, Rosenberg SA.
Science. 2015 Dec 11;350(6266):1387-90. doi: 10.1126/science.aad1253. Epub 2015 Oct 29.

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.
Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA.
Science. 2015 Apr 3;348(6230):124-8. doi: 10.1126/science.aaa1348. Epub 2015 Mar 12.

Interactions within the MHC contribute to the genetic architecture of celiac disease.
Goudey B, Abraham G, Kikianty E, Wang Q, Rawlinson D, Shi F, Haviv I, Stern L, Kowalczyk A, Inouye M.
PLoS One. 2017 Mar 10;12(3):e0172826. doi: 10.1371/journal.pone.0172826. eCollection 2017.

Chronic infectious disease and the future of health care delivery.
Farmer PE.
N Engl J Med. 2013 Dec 19;369(25):2424-36. doi: 10.1056/NEJMsa1310472. No abstract available.

Aspects of stochastic population dynamics in gene expression and cellular decision making

Michael Assaf (HUJI)

Cellular processes do not follow deterministic rules; even in identical environments, genetically identical cells can make random choices leading to different phenotypes. This randomness originates from fluctuations, both intrinsic and extrinsic, present in the biomolecular interaction networks. While for low-copy-number biomolecules intrinsic noise dominates, for high copy-numbers, extrinsic noise has been experimentally shown to dominate the variation. In this talk, I will review some recent works dealing with the stochastic dynamics of simple gene network motifs, focusing on those motifs that can be viewed as the building blocks of genetic switches.

I will dedicate the first part of the talk to presenting an analytical method for calculating statistics of large deviations in such systems, under intrinsic noise only. A notable example is the mean switching time between different (metastable) phenotypic states. The method will be demonstrated on two prototypical examples of genetic switches: a positive-feedback-based self-regulating gene, and a negative-feedback-based genetic toggle switch.

The second part of the talk will focus on the combined effect of intrinsic and extrinsic noise on simple gene expression motifs. I will present a theoretical framework that allows incorporating extrinsic noise to these systems by modeling bounded extrinsic noise as an auxiliary species in the master equation. The role of the extrinsic noise properties (magnitude, correlation time, and distribution) on the statistics of interest will be explored, and the effect of fluctuations in different reaction rates will be compared. Due to its analytical nature, our formalism can be used to improve the interpretation of data from single-cell gene expression experiments.

Related Research Questions

1. Why do individual identical cells behave differently under the same environment?
2. How accurate are cellular decisions in a given environment?
3. How can a cell population increase its robustness?

Suggested Reading

Stochastic gene expression in a single cell.
Elowitz, MB, Levine, AJ, Siggia, ED, Swain, PS (2002).
Science 297:1183–6.

Quantifying E coli proteome and transcriptome with single-molecule sensitivity in single cells.
Taniguchi, Y, Choi, PJ, Li, GW, Chen, H, Babu, M, Hearn, J, Emili, A, Xie, XS (2010).
Science 329:533–8.

Colored extrinsic fluctuations and stochastic gene expression.
Shahrezaei, V, Ollivier, JF, Swain, PS (2008).
Mol Syst Biol 4:196

Ecology resolves the complexity of immune self-tolerance

Uri Nevo (TAU)

Immune tolerance towards “self” is defined as the critical property of the immune system avoiding attack on cells of the host. Self-tolerance is reflected in multiple observations, sometimes contradictory. Thus, despite of 70 years of study, self-tolerance is yet regarded a complex and an enigmatic property of the immune system.

In the following lecture I will present the Ecoimmunity theory. Ecoimmunity abandons the classical dogma of immune unresponsiveness by deletion, suppression or ad-hoc regulation. Instead, the complexity of immune self-tolerance turns into a particular case of the universal predator-prey interaction. The theory further proposes that a lifelong interaction shaped mainly during early ontogeny, leads to selection of nonimmune cell phenotypes and facilitates immune-tissue homeostasis.

I will outline the basic principles of the theory and will describe surprising predictions and our supportive evidence obtained by a set of experiments

Related Research Questions

1. The immune system does not attack (it tolerates) the tissues of our body while attacking foreign pathogens (infectious bacteria/ viruses). How does the immune system tolerate (foreign) commensal bacteria?
2. If an autoimmune disease is a scenario where the immune system becomes unregulated and goes crazy, why in most cases does the immune system attack only one tissue?
3. If cells are organisms, where each acts as an independent agent, how do auto-reactive immune cells ‘agree’ to be turned off for their entire life time?

Suggested Reading

Experimental Support for the Ecoimmunity Theory: Distinct Phenotypes of Nonlymphocytic Cells in SCID and Wild-Type Mice.
Ochayon DE, Baranovski BM, Malkin P, Schuster R, Kalay N, Ben-Hamo R, Sloma I, Levinson J, Brazg J, Efroni S, Lewis EC, Nevo U.
Cell Transplant. 2016;25(8):1575-88.

The role of tissue adaptation and graft size in immune tolerance.
Hauben E, Roncarolo MG, Draghici E, Nevo U.
Transpl Immunol. 2007 Nov;18(2):122-5.

Ecoimmunity: immune tolerance by symmetric co-evolution.
Nevo U, Hauben E.
Evol Dev. 2007 Nov-Dec;9(6):632-42.

Cell-state organization: The living cell as a sloppy dynamical system

Erez Braun (Technion)

Biological cells present a paradox, in that they show simultaneous stability and flexibility, allowing them to adapt to new environments and to evolve over time. The emergence of a stable cell state, well-defined morphology, metabolism and function, depends on genotype-to-phenotype associations. These in turn essentially reflect the organization of gene regulatory modes determining the temporal spectrum of expressed proteins. Cell-state organization is a dynamical process in which the molecular disorder manifests itself in a macroscopic order. The genome does not determine the ordered cell state; rather, it participates in this process by providing a set of constraints on the spectrum of regulatory modes, analogous to boundary conditions in physical dynamical systems.

We have developed an experimental framework in which cell populations are exposed to unforeseen challenges; novel perturbations they had not encountered before along their evolutionary history. Our study of cell populations exposed some intriguing characteristics of their behavior, showing that cell-state organization reflects exploratory dynamics in a degenerate, high-dimensional phase-space. Thus, at the fundamental level, the living cell behaves similar to other exploratory biological systems, e.g., the nerve and immune systems. I'll discuss these exploratory dynamics, arguing that from the physics view point, the living cell belongs to a broad class of systems exhibiting sloppy dynamics, characterized by their insensitivity to the underlying parameters yet efficient convergence to a viable state. These concepts have significant consequences for our understanding of the emergence and stabilization of a cell phenotype in diverse biological contexts. In particular, understanding exploratory dynamics has implications on three major areas of biological inquiry: evolution, cell differentiation and cancer.

Related Research Questions

1. What are the relevant variables determining the state of the living cell?
2. How does order, a stable cell state, emerge from the intracellular molecular disorder?
3. What is the potential of cells to adapt to unforeseen challenges and what type of dynamics enable this potential?

Suggested Reading

The unforeseen challenge: from genotype-to-phenotype in cell populations
E. Braun
Rep. Prog. Phys. 78 (2015) 036602.

Deciphering the family tree of immune and blood cells

Leïla Perié (Institut Curie)

How heterogeneous systems of cells constituting multicellular organisms establish, organize and achieve coordination persists as a central question in natural sciences. Whereas stochastic gene or protein expressions have clearly demonstrated their role in cellular heterogeneity and are widely studied, the role of cell heterogeneity in the organization of multicellular organisms has been less interrogated. Addressing this question requires adequate tools that quantitatively study ensembles of cells individually rather than group of cells.

My research aims at addressing cell heterogeneity in dynamical and complex systems of cells using the hematopoietic system as a study model. Strikingly hematopoietic cells (immune cells, platelets and red blood cells) compose over 90% of total human cells and correspond to approximately ten trillions of cells (Sender R, 2016). More importantly they all originate from the same cells, the hematopoietic stem cells (HSC), through a process called hematopoiesis. In addition, as immune and blood cells have a short life span (from hours to months) and can response to perturbations like infections, this process is highly dynamical. It is therefore an interesting and challenging model to study how robust cell production is achieved in a complex system at the single cell level.

For this purpose, we combine different experimental and mathematical/computational approaches of single cell tracing to study hematopoiesis in vivo. Cellular barcoding is one of these lineage tracing approaches that allow to simultaneously traces the in vivo differentiation of individual cells, allowing to reconstitute the relationship between cell lineages with single cell resolution. In this seminar, I will discuss some of our recent results using cellular barcoding.

Related Research Questions

1. How do (immune) cells undergo differentiation? How is robust production of cells generated?
2. What are the steps of differentiation? When is the fate decision made? Does it involve intrinsic, extrinsic or stochastic mechanism?

Suggested Reading

Cellular barcoding: a technical appraisal.
Naik SH ,Schumacher TN , Perié L.
Exp Hematol.
2014 Aug;42(8):598-608. doi: 10.1016/j.exphem.2014.05.003. Epub 2014 Jul 1.

Retracing the in vivo haematopoietic tree using single-cell methods.
Perié L, Duffy KR.
FEBS Lett.
2016 Nov;590(22):4068-4083. doi: 10.1002/1873-3468.12299. Epub 2016 Jul 26.

Deciphering the structural design principles for interaction specificity among signaling proteins

Mickey Kosloff (Haifa U)

For cellular signaling cascades to function correctly, their protein components must recognize their appropriate partners accurately. This requirement presents a challenge for living cells, as related components are used repeatedly in both parallel and intersecting cascades within the same cell. Signaling therefore requires that the interactions of particular protein-family members be tailored to each signaling cascade via interaction specificity. Understanding the structural "code" for such selectivity is a major goal in both experimental and computational biology, as well as in drug design. Yet, beyond single representative examples, little is known of how specificity is determined among members of large protein families, including those involved in signal transduction. Of particular interest to our lab are the ubiquitous protein super-families involved in G protein coupled signaling and tyrosine kinase dependent signaling.

We developed a "bottom-up" approach that utilizes energy calculations of multiple 3D structures to decipher interaction specificity. We integrate these calculations with biochemical and biophysical results to map specificity determinants at the protein family level and at the resolution of individual amino acids. The resulting "residue-level maps" are then used to redesign proteins with altered activities and specificities, offering new insights into protein-protein interactions. This also paves the way for the engineering of signaling networks at the cellular level and for developing better drugs that take family-level specificity into account.

Related Research Questions

1. How do structurally-similar proteins encode for common function yet different specificities?
2. How do structurally-dissimilar proteins encode for similar specificities for a common target?
3. How does specificity "wire" together signaling networks?

Suggested Reading

Integrating energy calculations with functional assays to decipher the specificity of G protein-RGS protein interactions.
Kosloff M, Travis AM, Bosch DE, Siderovski DP, Arshavsky VY.
Nat Struct Mol Biol. 2011 Jun 19;18(7):846-53

From Protein Structure to Function via Computational Tools and Approaches
Rachel Kolodny, Mickey Kosloff
Isr. J. Chem., 53: 147–156

Epigenetics and expression heterogeneity in mouse embryonic stem cells

Eran Meshorer (HUJI)

Pluripotent self-renewing embryonic stem cells (ESCs) have been the focus of a growing number of high-throughput experiments, revealing the genome-wide locations of hundreds of transcription factors and histone modifications. While most of these datasets were used in a specific context, all datasets combined offer a comprehensive view of chromatin characteristics and regulatory elements that govern cell states. We recently assembled all published genome-wide ChIP experiments in mouse and human ESCs into a searchable database and webtool allowing epigenomic analysis (Livyatan et al., Cell Stem Cell, 2015). Using these hundreds of datasets in ESCs, we generated colocalization maps of chromatin proteins and modifications, and built a discovery pipeline for regulatory proteins of gene families. We define alternative promoters of pluripotency factors, provide an expanded epigenetic profile for lincRNA genes beyond the basal ‘‘K4–K36’’ and detect subclasses of lincRNAs that may be indicative of their potential function, and offer an Enhancer Finder function which scans the upstream region of any given gene for potential regulatory elements. By comparing genome-wide binding data with over-expression and knockdown analysis of hundreds of genes, we discovered that the pluripotency-related factor Nr5a2 separates mitochondrial from cytosolic ribosomal genes, regulating their expression. We further show that genes with a common chromatin profile are enriched for distinct Gene Ontology (GO) categories. By combining these data with single cell RNA-sequencing (scRNA-seq) data, we were able to assign an epigenomic signature for heterogeneous and stable genes in ESCs. Our approach can be generalized to reveal common regulators of any gene group; discover novel gene families, and identify common genomic elements based on shared chromatin features.

Related Research Questions

1. Do epigenetic profiles of gene families provide functional information beyond expression?
2. Is expression heterogeneity regulated at the epigenetic level?
3. Can we systematically identify transcription factors regulating heterogeneous expression?

Suggested Reading

Studying lineage decision-making in vitro: emerging concepts and novel tools.
Semrau S and van Oudenaarden A (2015)
Annu Rev Cell Dev Biol.31:317-45

BindDB: An integrated database and webtool platform for "Reverse-ChIP" epigenomic analysis.
Livyatan I, Aaronson Y, Gokhman D, Ashkenazi R, Meshorer E (2015)
Cell Stem Cell, 17(6):647-8

Systematic identification of gene family regulators in mouse and human embryonic stem cells.
Aaronson Y, Livyatan I, Gokhman D, Meshorer E (2016)
Nucleic Acids Res.,44(9):4080-9

Cellular heterogeneity in kidney tissues and tumors

Tomer Kalisky (BIU)

A major challenge in stem cell biology is to identify and molecularly characterize tissue-specific stem cells in tissues and tumors. In cancer, this is especially challenging since stem cells usually consist a very small fraction of the tumor "bulk". To this end we used a combination of single cell technologies and next-generation sequencing to measure gene expression and sequence information from hundreds of individual cells in order to identify and molecularly characterize the cell sub-population repertoire of a developing fetal kidney (in both human and mouse) and Wilms' tumor - a pediatric kidney tumor thought to originate from faulty differentiation of fetal developing tissues. We find that Wilms' tumor is composed of cells resembling the most immature cell types of the developing fetal kidney. Moreover, we find that not one – but two populations are required for tumor initiation, suggesting that distorting the communication between these populations might pave the way for a cure. Finally, we show that different Wilms' tumors create a continuum in gene expression space between archetypes that correspond to distinct cell types in the developing kidney.

Related Research Questions

1. What are the main cell types that co-exist within the developing and adult kidney and what are the relations between them?
2. How do these cell types change over the lifetime of the organism (pre-birth to adulthood) and how are they distorted in disease?
3. Can we find unique markers for cancer stem cells? (both pediatric and adult tumors)

Suggested Reading

Kidney Development: Two Tales of Tubulogenesis
M. Little, K. Georgas, D. Pennisi, and L. Wilkinson
Current Topics in Developmental Biology, vol. 90, B. A. Thornhill and R. L. Chevalier, Eds. 2010, pp. 193–229.

Geometry of the Gene Expression Space of Individual Cells
Y. Korem, P. Szekely, Y. Hart, H. Sheftel, J. Hausser, A. Mayo, M. E. Rothenberg, T. Kalisky, and U. Alon
PLOS Comput. Biol., vol. 11, no. 7, p. e1004224, 2015.

Single-cell dissection of transcriptional heterogeneity in human colon tumors
P. Dalerba, T. Kalisky, D. Sahoo, P. S. Rajendran, M. E. Rothenberg, A. a Leyrat, S. Sim, J. Okamoto, D. M. Johnston, D. Qian, M. Zabala, J. Bueno, N. F. Neff, J. Wang, A. a Shelton, B. Visser, S. Hisamori, Y. Shimono, M. van de Wetering, H. Clevers, M. F. Clarke, and S. R. Quake
Nat. Biotechnol., vol. 29, no. 12, pp. 1120–1127, 2011.

Exploratory Adaptation in Gene Regulatory Networks

Naama Brenner (Technion)

The capacity of cells and organisms to respond in a repeatable manner to challenging conditions is limited by a finite repertoire of adaptive responses. Beyond this capacity, novel and unforeseen challenges may elicit exploratory dynamics, improvisational in nature, which could provide response to a much broader array of conditions. However little is known about such exploration, its dynamics and its ability to converge to a new stable cell state.

I will review recent experiments on adaptation to unforeseen challenges. I will then describe a model of a gene regulatory network inspired by these experiments, which can converge to new adapted stable states by purely stochastic exploration. Such convergence is not guaranteed in a high-dimensional space, and indeed is not universal. Successful convergence requires outgoing hubs in the network, and is enhanced by their auto-regulation. Since these are both well-known properties of gene regulatory networks, these findings establish a basis for a biologically plausible mode of adaptation by exploratory dynamics.

Related Research Questions

1. Gene regulation exhibits plasticity and generates novelty along evolution; how can these properties be exposed and studied in the lab?
2. What are the characteristics and principles of exploratory dynamics resulting from this plasticity in gene regulatory networks?
3. What allows the convergence of exploratory adaptation in the high-dimensional space of gene interactions? And how is this process related to learning?

Suggested Reading

Genome-wide transcriptional plasticity underlies cellular adaptation to novel challenge
S. Stern, T. Dror, E. Stolovicki, N. Brenner and E. Braun
Mol. Sys. Biol. 3, article #106 (2007). See also commentary by E.V. Koonin, Mol. Sys. Biol. 3, article # 107 (2007).

Exploratory adaptation in large random networks
H. Schreier, Y. Soen and N. Brenner
Nature Communications 8, 14826 (2017).

The unforeseen challenge: from genotype-to-phenotype in cell populations.
E. Braun.
Reports on Progress in Physics, 78(3):036602, 2015.

A principle of organization which facilitates broad lamarckian-like adaptations by improvisation.
Y. Soen, M. Knafo, and M. Elgart.
Biology direct, 10(1):1, 2015.

Building Models for Understanding and Engineering Gene Expression Dynamics

Tamir Tuller (TAU)

Gene expression is a fundamental process that occurs in all cells and is related to all biomedical phenomena. Gene expression is encoded in different parts of the genome in a non-modular manner and based on organism specific codes. Thus, today we understand only a small fraction of the gene expression codes, and most of the gene expression models are very partial and can provide very limited predictions. In our research we aimed at developing generic/universal approaches for understanding, modeling and engineering the way gene expression is encoded in the genetic material. In this talk I will review our multidisciplinary strategy and concepts, and some recent key results. Among others, I will describe whole cell biophysical simulations of translation, and unsupervised information theoretic approaches for gene expression modeling. I will demonstrate how these tools can help us understand fundamental phenomena in molecular evolution and functional genomics, and will demonstrate some biotechnological applications related to our models.

Related Research Questions

1. How silent mutations in the transcript constrain and effect its evolution?
2. Is it possible to map sub-sequences of the genetic material to complex biophysical aspects of gene expression?
3. Is it possible to automatically decipher and engineer gene expression aspects?

Suggested Reading

http://www.cs.tau.ac.il/~tamirtul/Selected_publications/NAR-2017.pdf

http://www.cs.tau.ac.il/~tamirtul/Selected_publications/Interface2016.pdf

http://www.cs.tau.ac.il/~tamirtul/Selected_publications/RNA_BIOL_2015.pdf

http://www.cs.tau.ac.il/~tamirtul/Selected_publications/NAR2015.pdf

http://www.cs.tau.ac.il/~tamirtul/Selected_publications/Bioinformatics2014.pdf

Challenges in extracting splicing bias from single cell RNA sequencing data

Tal Shay (BGU)

Hematopoietic stem cells (HSCs) differentiate into all blood and immune cell types. As a population, HSCs express many genes, and for the vast majority of those genes, many isoforms. Single cell RNA sequencing (scRNA-seq) has revolutionized the understanding of cell population heterogeneity in many biological systems. In particular, for HSCs, scRNA-seq revealed lineage priming, clonality, and differentiation trajectories. However, the isoform usage at the single HSC level and its regulation are still unknown.

We collected publicly available murine HSCs scRNA-seq datasets and identified genes for which HSCs display splicing bias, where the single cell splicing isoforms usage is significantly different from the population level usage. Apparent splicing bias can be affected by amplification bias, random loss of molecules, low coverage and other technical factors. As splicing bias is consistent between datasets produced by scRNA-seq protocols, it seems to reflect a real biological bias of the cells, whose regulation and functional consequence remains to be studied.

Related Research Questions

1. What are the regulatory mechanism of RNA splicing?
2. Is the splicing isoforms mixture in each cell a random sample of the splicing isoforms mixture of the cell population?
3. Is the splicing isoforms mixture in each cell stochastic or regulated?

Suggested Reading

https://en.wikipedia.org/wiki/RNA_splicing

https://en.wikipedia.org/wiki/Alternative_splicing

Computational and analytical challenges in single-cell transcriptomics
O. Stegle, S. A. Teichmann, J. C. Marioni
Nature Reviews Genetics 16, 133–145 (2015)

The origins of cellular selection in adaptive immunity

Martin Flajnik (University of Maryland)

Often overlooked in the origins of adaptive immunity, secondary lymphoid organs (SLO) play a major role in the generation of high affinity immune responses. The spleen is the oldest SLO, first appearing in the jawed vertebrates (gnathostomes, the oldest living group the cartilaginous fish), having a segregation of B and T cell zones. We have shown recently that there is a single population of antigen presenting cells (APC) in amphibians, which can present antigen to both B and T cells (the so-called "XL cell"). After immunization with a foreign antigen, these APC were shown to display antigen on their surface, probably in the form of immune complexes and covalently-bound complement, and they migrate into B cell zones in a T cell-dependent manner. XL cells are of a hematopoietic origin and bear high levels of MHC class II molecules, which also have them poised to present antigens to T cells. We propose that these APC perform a 'double-duty,' presenting antigen to both T cells and B cells in the course of a response. A model will be presented in which antigen is first presented to T cells, and then activated T cells license the same APC to present cell-bound antigen to B cells. A large leap forward in evolution, therefore, occurred in mammals with the appearance of follicular dendritic cells (FDC), non-hematopoietically derived APC that reside perpetually in B cell follicles, orchestrating the maintenance of the B cell follicle as well as the formation of germinal centers. Thus, although somatic hypermutation and antigen selection arose at the origins of adaptive immunity, the division of labor between two types of APC, conventional DC and FDC, provided another tier to the ability of the immune system to mutate and select high affinity B cell clones. Jawless fish, which have an adaptive immune system based on a convergent set of antigen receptors (the VLR), have T and B cells as well, but no known SLO. It is a challenge to understand how these vertebrates are able to make efficient immune responses.

Related Research Questions

1. The tumor necrosis factor (TNF)-related cytokines lymphotoxins (LT) are crucial for the formation of FDC and germinal centers. Cold-blooded vertebrates lacking FDC nevertheless have these cytokines (encoded within the MHC). What might be the primordial functions of LT in these animals?
2. In the absence of germinal centers, some ectothermic vertebrates are capable of selection of high affinity antibodies with marks of positive selection. How might this be achieved, i.e. what testable hypothesis could we put forward?
3. Even when SLO are absent, in the case of jawless fish, B cells seem to undergo somatic mutation and some level of selection. What can explain this phenomenon?

Suggested Reading

Emergence and Evolution of Secondary Lymphoid Organs
Harold R. Neely and Martin F. Flajnik
Annual Review of Cell and Developmental Biology Vol. 32:693-711 (Volume publication date October 2016)

Learning from antibodies how to design new protein functions

Sarel Fleishman (Weizmann)

Computational protein design holds the promise of programming a new generation of enzymes and therapeutics with desired qualities such as affinity, specificity, and stability. Protein design studies have so far mostly focused on the fundamental question of how to design new protein folds using atomistic design simulations . Success in designing new molecular functions, however, has been much more limited. To address this gap, we have looked to immune-system antibodies, which are the most versatile class of binding molecules in nature, and inferred general principles for designing stable and specific binders. Our design strategy is unique in combining evolutionary principles with atomistic modeling; it uses commonly observed backbone conformations and sequence patterns in order to design new antibodies . The resulting antibodies, though very different from any mammalian germline, show the same desirable features, such as high stability, affinity, and specificity. Furthermore, experimental structures show that the design models are atomically accurate, suggesting that future antibodies may be designed completely by computer. We moreover show that the design principles we inferred are general, and can be applied to substantially improve the stability and activity of challenging eukaryotic proteins, including the leading malaria vaccine candidate, the Plasmodium falciparum RH5 protein. In unpublished results, we have also designed new enzymes and novel high-dimensionality specificity networks. We therefore conclude that the synergy between evolutionary principles and atomistic design calculations can resolve some of the most recalcitrant problems in protein engineering and design.

Related Research Questions

1. What is the molecular architecture of a protein active site (in enzymes or binders), and what differentiates it from other parts of the protein?
2. Why is it so much more difficult to design active sites than other parts of the protein?
3. Why are natural proteins in mesophiles often only marginally stable, whereas thermophiles exhibit homologous and functionally equivalent proteins that are hyperstable?

Suggested Reading

Role of the biomolecular energy gap in protein design, structure, and evolution.
Fleishman, S.J. & Baker, D. (2012).
Cell 149, 262–273

Why reinvent the wheel? Building new proteins based on ready-made parts.
Khersonsky, O. & Fleishman, S.J. (2016).
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Automated Structure-and Sequence-Based Design of Proteins for High Bacterial Expression and Stability.
Goldenzweig, A., Goldsmith, M., Hill, S.E., Gertman, O., Laurino, P., Ashani, Y., Dym, O., Unger, T., Albeck, S., Prilusky, J., Lieberman, R.L., Aharoni, A., Silman, I., Sussman, J.L., Tawfik, D.S. & Fleishman, S.J. (2016). Mol. Cell 63, 337–346

Can we predict the evolution of viruses?

Adi Stern (TAU)

Predicting the course of evolution is one of the most challenging and potentially important areas in biology. The process of evolution can be decomposed into two components: the deterministic action of selection, and stochastic effects manifested as genetic drift. In my talk I will discuss how we tease apart the effects of selection from genetic drift, and I will present evidence of extensive parallel substitution and recombination events occurring in repeated epidemics of vaccine-derived polioviruses. The mutations and the evolutionary trajectories driving these epidemics were replicated using a simple cell-based experimental setup where the rate of evolution was intentionally accelerated. Furthermore, mutations accumulating during epidemics increased the replication fitness of the virus in cell culture and increased virulence in an animal model. This study provides a powerful framework for rational design of safer vaccine strains and for forecasting virulence of viruses.

Related Research Questions

1. Is it possible to forecast the next virus epidemic?
2. What is the role of chance versus causality in viruses?
3. How many viable evolutionary trajectories can viruses explore?

Suggested Reading

The Evolutionary Pathway to Virulence of an RNA Virus.
Stern, A., Yeh, M.T., Zinger, T., Smith, M., Ling, G., Nielsen, R., Macadam, A., Andino, R.
Cell, Volume 169, Issue 1, 23 March 2017, Pages 35–46.e19

What can we predict about viral evolution and emergence?
Holmes, E.
Curr Opin Virol. 2013 Apr; 3(2): 180–184.

Immune balance: Towards a dynamic view of immune behavior

Bartlomiej Swiatczak (University of Haifa)

The last two decades of research revealed that mutualistic microbes play an important role in the maintenance and construction of the organism by engaging in a variety of developmental, metabolic and defense functions. Accordingly, the question of mechanisms that mediate tolerance to mutualistic microbes and rejection of pathogenic ones became of crucial importance. Despite significant efforts to understand how the immune system tells friends from foes to permit survival of the communities beneficial to the organism, this discrimination remains elusive. Perplexingly, pathogens and commensals were found to stimulate the same types of immune receptors and to induce similar molecules, many of which are instruments of defense. In this presentation I refer to the century old notion of immune equilibrium to suggest that the essence of microbe-host relationship lies in its dynamics and that the role of the immune system is to sense and modulate this dynamic by promoting stable interactions with whatever the system encounters, including microbes, self-cells and foreign cells. From this point of view, the question of how mutualistic microbes are tolerated and pathogenic ones rejected cannot be separated from the question of how tolerance mutualizes microbes and rejection pathogenizes them.

Related Research Questions

1. How does the immune system manage to protect the host from an infection if pathogens fail to exhibit structural features unique to them?
2. How do host-derived and microbe-derived factors intermingle to establish the role of microbial colonizers as pathogens or commensals?
3. How does the interdependence of IgA antibody populations and luminal microbial populations establish microbe-host mutualism?

Suggested Reading

Immune balance: the development of the idea and its applications
Swiatczak B. 2014
Journal of the History of Biology 47: 411-42.

Gut feelings of safety: tolerance to the microbiota mediated by innate immune receptors
Swiatczak B, Cohen IR. 2015
Microbiology and Immunology 59: 573-85.