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Current Opinion in Systems Biology

Balancing robustness and evolvability in single cells and beyond

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Abstract

Robustness and evolvability are defining properties of biological systems. Robustness promotes reproducibility of central biological functions, primarily by maintaining low mutation frequency and small mutational effects. By contrast, evolvability is possible only when mutations are frequent enough and lead to selectable functional effects. What is the tradeoff between robustness and evolvability? Here, we explore several cellular strategies used to regulate the balance between robustness and evolvability by modulating mutational impact or frequency. These mechanisms span the gene promoter level, biochemical pathways, single cell and whole organism levels. In particular, we discuss a recently discovered mechanism implemented at the level of single cells, in which phenotypic stress-persistence and DNA damage are mechanistically coupled. This coupling increases genetic diversity specifically among individual cells that survive harsh conditions, in which evolvability may be beneficial. Taken together, these mechanisms suggest that robustness and the ability to tune mutation effects, promotes, rather than limits, the capacity to evolve.

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Current Opinion in Systems Biology 2018, ■:1–6

This review comes from a themed issue on **Special Section: Single cell and systems biology(2018)**

Edited by **Frank J. Bruggeman and Peter Swain**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.coisb.2018.02.008

Introduction

Biological systems show a remarkable capacity to maintain proper function in a wide range of environments, despite stochastic fluctuations in gene or protein levels, or significant genetic variations. Implicated in this ability are the two general, but seemingly contrasting principles: *robustness* and *evolvability*: Robustness denotes the low sensitivity of key phenotypes to environmental or genetic variations. A key example is the body pattern, whose shaping during embryonic development in highly reproducible between individuals, despite significant environmental and genetic differences [1]. The second principle, *evolvability*, denotes the ability of biological systems to optimize their phenotypes in accordance with changing requirements through mutation-selection processes. Robustness therefore maintains existing functionality in a wide range of conditions by buffering the phenotype against variations, whereas evolvability aims to enhance functionality by adjusting the relevant phenotypes with the changing conditions.

The principles of robustness and evolvability present alternative strategies for dealing with uncontrolled variability. Their relative advantage depends on the particular phenotype, and on the perturbation with which cells or organisms are presented. The molecular basis and requirements promoting robustness or evolvability differ. Robustness benefits from low mutational effects, whereas evolvability relies on mutations having significant effects. This raises the question of whether robustness and evolvability compete with each other, so that increasing robustness necessarily limits evolvability, or whether they may in fact co-exist or even promote each other.

Tradeoff between robustness and evolvability inevitably exist in some cases. Consider for example the case of proofreading during DNA replication that by first approximation lowers the mutation rate (and hence evolvability) while promoting robustness. Recent theories have addressed tradeoffs, using concepts such as Pareto optimality to obtain insights into the quantitative relationship between phenotypic tradeoffs and how they shape evolution [2,3].

In this review, we describe specific mechanisms by which cells co-optimize robustness and evolvability. These mechanisms include modulating the impact of mutations on different genes or processes, or changing the frequency of mutations as a function of the environmental or genetic condition. We focus in particular on our recent report, describing a coupling between phenotypic persistence and DNA damage, which we propose fits into this paradigm [4].

Buffering mutation effects: robust wiring of biochemical circuits

Most biological functions, and in particular those involving information processing, are executed by networks of interacting genes and proteins. The relevant phenotype is therefore defined as an emergent property

of the circuit, and is not associated with a single gene or protein. A principle mode by which robustness is maintained is through circuit wirings that minimize the sensitivity of key outputs towards variations in the biochemical parameters defining circuit dynamics. Such robust wiring buffers key phenotypes against environmental changes or genetic mutations that impact the associated biochemical parameters [5]. One example for this principle was demonstrated in bacterial chemotaxis, where precise adaptation of the sensory-receptors signaling activity is a key property that is maintained robust by virtue of a specific circuit design [6,7]. Other key examples come from developmental patterning, where robustness (also termed canalization) is extensively studied [8–14]. Circuits that pattern tissues and organs are wired to limit sensitivity to the dosage of the patterning genes, the overall size of the tissue or to other parameters defining patterning dynamics.

It would appear that robust circuit design can limit the capacity to evolve, since mutation effects are buffered. However, robustness is typically confined to certain key properties, while other properties retain their sensitivity to mutations and can therefore readily adapt to changes. We argue that this flexible design – ensuring the robustness of some properties while allowing others to evolve – may in fact promote, rather than limit evolvability [15]. Consider the case of bacterial chemotaxis. Here, the ability of the sensory receptors to precisely adapt their signaling activity is a robust property, but the adapted level remains highly sensitive to biochemical parameters. It therefore becomes relatively easy to evolve the chemotaxis system by adjusting the steady state level to the changing requirement, while maintaining the optimized chemotactic ability.

Similarly, robustness of body patterning circuits may also promote evolvability. This becomes apparent when considering the relation between pattern and size. Since size is highly variable between individuals, robust patterning entails the adjustment (or scaling) of pattern with size, to maintain proportionality of the different tissues [16–20]. Scaling mechanisms have therefore evolved to ensure robustness to size-varying mutations. Notably, this scaling property promotes evolvability of size, as in the absence of robust scaling, mutations that alter size will also alter body pattern, likely leading to deleterious consequences even if the altered size were advantageous. By contrast, in the presence of robust scaling, the body pattern will automatically adjust to the new size, enabling fixation of size-varying mutations.

Regulating mutation effects in a gene-specific manner – flexible vs. stable promoter structures

Robust wiring of biochemical circuitry buffers specific functional outputs against mutations, while maintaining evolvability of other phenotypes. Here, while mutations still have an effect on protein expression or function, these effects are buffered via circuit wiring. A complementary strategy is to buffer the effect of the mutation at the single gene or protein level. Here, the balance between robustness and evolvability could be maintained by mechanisms that modulate the effect of mutations in a gene-specific manner, maintaining low mutation sensitivity of e.g essential genes, while allowing high sensitivity to mutations at environmental-responsive genes.

This principle is exemplified by studies of gene expression, which revealed that genes differ greatly in their *expression flexibility*. This flexibility of expression can be measured on various time scales: stochastic variations (noise) between genetically identical individual cells growing in the same conditions, response to changing conditions, or diversity between strains or species. Notably, these three rather distinct measures are highly correlated: 'noisy' genes are also highly responsive to changing conditions and further diverge more rapidly across species. Furthermore, expression of these genes is more sensitive to mutations in their promoters, rendering them more evolvable [21–25].

The key determinant of expression flexibility is the gene promoter. Two typical promoter structures have been described, that are respectively associated with low or high expression flexibility. The first class ("DPN: Depleted Proximal Nucleosome") displays a well-defined nucleosome free region (NFR) close to the transcription start site and lacks a TATA box, while the second class ("OPN: Occupied Proximal Nucleosome") lacks this NFR but has a TATA box. A continuous measure positions each gene along the OPN-DPN axis. This measure strongly correlates with expression flexibility, with OPN genes being most flexible and DPN most stable. Therefore, this promoter design modulates the flexibility of gene expression and thus its sensitivity to mutations [23]. Using these promoter architectures, cells can tune the sensitivity of gene expression to promoter mutations, maintaining some genes robust to such mutations, while allowing rapid evolvability in others.

Regulating mutation effects in a condition-specific manner

In addition to tuning mutation sensitivity between genes or processes, it may also be beneficial to modulate this sensitivity in a condition-dependent manner. Indeed, growth in many conditions has been optimized by evolution, in which case mutations are most likely to be deleterious. Other conditions, in particular extreme or stressful environments, may however still benefit from higher mutation rate. The concept of buffering mutational effects in 'normal' conditions, while