use this framework to address three fundamental questions: (i) when a cell should prefer thresholding to a graded response; (ii) when there is a fitness advantage to implementing a Bayesian decision rule; and (iii) when retaining memory of the past provides a selective advantage. We specifically find that: (i) relative convexity of enzyme expression cost and benefit influences the fitness of thresholding or graded responses; (ii) intermediate levels of measurement uncertainty call for a sophisticated Bayesian decision rule; and (iii) in dynamic contexts, intermediate levels of uncertainty call for retaining memory of the past. Statistical properties of the environment, such as variability and correlation times, set optimal biochemical parameters, such as thresholds and decay rates in signaling pathways. Our framework provides a theoretical basis for interpreting molecular signal processing algorithms and a classification scheme that organizes known regulatory strategies and may help conceptualize heretofore unknown ones.

1831-Plat
Fundamental Constraints on the Abundances of Chemotaxis Proteins
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Flagellated bacteria, such as *Escherichia coli*, perform directed motion in gradients of concentration of attractants and repellents in a process called chemotaxis. Transmembrane chemoreceptors, which bind attractants and repellents, control the activity of the histidine kinase CheA, which phosphorylates the cytoplasmic response regulator CheY. Phosphorylated CheY binds to FliM in the flagellar motors. This binding controls the direction of the rotation of the motors, and hence the motion of the cell.
E. coli chemotaxis is a model for signal transduction. However, this signaling system features very large abundances of the proteins involved, compared to those of analogous or homologous systems. Estimating the timescales of the pathway enables us to trace the need for this large number of chemotaxis proteins to the specific requirement of the chemotaxis system for fast response. We also show that further constraints arise from the requirements of self-assembly, both of flagellar motors and of chemoreceptor arrays.
A surprising fact is that the abundance of all the chemotaxis proteins significantly increases in poorer medium, while their proportions are conserved. Artificially over-expressing chemotaxis proteins in a concerted manner has been shown to increase chemotactic efficiency. Employing a chemotaxis pathway model, we show that the gain of the pathway at the level of the response regulator CheY increases upon concerted over-expression of the chemotaxis protein abundances. This increase of the gain could allow cells to become sensitive to even smaller changes of concentrations of attractant, which may be beneficial in poor nutritional conditions. Besides, over-expression yields higher cooperativity of receptor teams, which could further contribute to increasing the sensitivity of the pathway. We also demonstrate that physiological proportions yield near-optimal gain, and that the pathway is robust to variations in abundance of the motor protein FliM.

1832-Plat
Early Lineage Bifurcation during Differentiation of Embryonic Stem Cells Revealed by Single-Cell Transcriptomics
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The development of more efficient and specific in vitro differentiation protocols is hampered by the inherently heterogeneous cellular response to lineage specifying signals. Here, we used our recently developed single-cell RNA-seq method [1] and single-molecule FISH [2,3] to quantify the variability in transcriptional states of thousands of individual mouse embryonic stem cells during differentiation with retinoic acid. After a fast initial response cells exhibited delayed commitment to differentiation followed by a bifurcation into an ectoderm-like and an extraembryonic endoderm-like transcriptional state. Notably, many cells assumed an extraembryonic endoderm-like state through an ectoderm-like intermediate. In contrast to the current belief that cells are initially refractory to lineage specifying signals we found that an early, short retinoic acid pulse was able to influence the lineage decision while the cells were not yet committed. Additionally, gene expression variability, as quantified by the entropy per gene, showed a non-trivial dynamical behavior: while the accepted paradigm states that the entropy of the whole system should decrease monotonically during differentiation, we found that the average entropy per gene first decreased before it increased towards its global maximum at the end of the differentiation time course. Interestingly, this variability ''bottleneck'' coincided with the point of commitment beyond which cells were not able to return to their pluripotent initial state. In conclusion, our study demonstrated that the first few hours of a differentiation protocol can be critical for the lineage decision. This observation is vital for the scientific community interested in improving differentiation protocols.
[1] Soumillon, Cacchiarelli, Semrau et al., 2014, biorxiv: http://dx.doi.org/10.1101/003236 (under review)
[2] Raj et al., Nat Methods, 2008, vol. 5 (10), pp. 877-879
[3] Semrau et al., Cell Reports, 2014, vol. 6 (1), pp. 18-23

1833-Plat
Emergent Behaviours of Stem Cells in Organogenesis Demonstrated by Hybrid Modelling
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The development of organs from stem cells is a complex process determined by spatial and temporal control mechanisms, to create well defined and complex 3D structures. In this process, a homeostasis between the processes of cell division and cell death is required. Executable biological models describe signalling and developmental processes at a high level of abstraction, allowing for mechanistic behaviour to be modelled in the absence of precise kinetic information. However, the physical process of 3D growth in the development of an organ is harder to abstract. Here we present a hybrid model of the development of the C. elegans germline from a pool of stem cells. The model combines a description of signalling and developmental processes using an executable model, developed in the BioModelAnalyzer tool (http://biomodelanalyzer.research.microsoft.com/), with a physical model of cell interactions described using Brownian dynamics simulation. This tool uniquely allows us to study the dynamics of organ development and growth, and here we will present new predictions arising from this model. We show how thermal mixing of the stem cell population presents a barrier to clonal dominance through tracking of cell lineages. By abstracting the new model, we demonstrate how invariant fate progression in developing cells is achieved in a complex, multi-stable system. Finally, we use the model to explore how different physical mechanisms of cell signalling, division and apoptosis are compatible with known behaviours.

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Phage DNA Dynamics in Correlation with Cell Fates
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Bacteriophage lambda begins its infection cycle by ejecting its DNA into its host E. coli cell, after which either the lytic or lysogenic pathway is chosen, resulting in different cell fates. In this study, using a new technique to monitor the spatiotemporal dynamics of the phage DNA in vivo, we found that the phage DNA moves via two distinct modes: localized motion and motion spanning the whole cell. One or the other motion is preferred depending on where the phage DNA is ejected into the cell. Through the phage DNA trajectories, we quantified the diffusion coefficient. Moreover, phage DNA motion is the same in the early phase of the infection cycle, irrespective of whether the lytic or lysogenic pathway is followed; hence, cell-fate decision-making appears not to be correlated with the phage DNA motion. However, after the cell commits to one pathway or the other, phage DNA movement slows during the late phase of the lytic cycle and remains the same during the entire lysogenic cycle. Throughout the infection cycle, phage DNA prefers the regions around the quarter positions of the cell.

1835-Plat
Systems Mechano-Biology: Tension-Inhibited Protein Turnover is Sufficient to Physically Control Gene Circuits
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Mechanotransduction pathways convert forces that stress and strain structures within cells into gene expression levels that impact development, homeostasis, and disease. The levels of some key structural proteins in the nucleus, cytoskeleton, or extracellular matrix have been recently reported to scale with tissue- and cell-level forces or mechanical properties, and so the mathematics of mechanotransduction becomes important to understand. Here, we show that if a given structural protein positively regulates its own gene expression, then stresses need only inhibit degradation of that protein in order to achieve stable, mechanosensitive gene expression. This basic 'use it or lose it' module is illustrated by application to meshworks of nuclear lamin A, mini-filaments of myosin II, and extracellular matrix collagen fibers - all of which possess filamentous coiled-coil/supercoiled structures. Past experiments not only suggest that tension suppresses protein degradation mediated and/or initiated by an enzyme, but also that transcript levels vary with protein levels as key transcription factors are regulated indirectly by these structural proteins. Coupling between modules