Fluctuations and Correlations in Physical and Biological Nanosystems: The Tale Is in the Tails

Michael L. Simpson[†,‡,*] and Peter T. Cummings[†,§,*]

[†]Center for Nanophase Materials Sciences, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831-6494, United States,
[‡]Department of Materials Science and Engineering, University of Tennessee, Knoxville, Tennessee 37996, United States, and
[§]Department of Chemical and Biomolecular Engineering, Vanderbilt University, Nashville, Tennessee 37235-1604, United States

ABSTRACT The inherently small system sizes involved imply that, in the absence of large applied fields designed to overwhelm them, fluctuations will play a major role in determining the response and functionality of nanoscale systems. Theoretical advances over the past two decades have provided fresh insight into fluctuations and their role at the nanoscale, even in the presence of arbitrarily large applied external fields. In contrast to traditional engineered systems, Nature's approach to nanotechnology is to embrace and to exploit fluctuations and noise to create adaptable, persistent, optimized functional architectures. We describe some of the mechanisms by which Nature exploits noise, with the goal of applying these lessons to engineered physical and chemical nanosystems. In particular, we emphasize the critical role of the tails of distributions of properties in both physical and biological nanosystems and their impact on system behavior.

The vision of the nanoscience revolution is to create new systems with functionality that greatly exceeds that possible with microscale technology, which has been stunningly successful in recent decades. As one example, consider the microelectronics revolution that began with the introduction of integrated circuits. Gordon Moore's 1965 observation[1] that microprocessor speed increased every 18−24 months as a result of the doubling of the number of circuit elements in a fixed area, thus allowing both clock speeds and compute capabilities to increase, has reached the level of technology law (Moore's Law). Microelectronics has been based on two fundamental concepts: creating structures by top-down methods (multiple lithography-based etchings of silicon interspersed with deposition steps) and, in operation, overcoming parasitic losses (due to noise and resistances) by driving the systems at high voltages across components. We can think of this (top-down design/fabrication, combined with application of forces large enough to overpower stochasm and thus achieve deterministic behavior) as typical of many artificial (man-made) systems, and it is a paradigm not limited to microeletronics; for example, modern aircraft are designed to expend tremendous amounts of energy to create deterministic, predictable behavior in flight. This artificial approach is consistent with magnification, not miniaturization: in aircraft, greater energy efficiency per person moved is achieved by making planes larger. In contrast, in nanotechnology, we strive to embrace Nature's quite different paradigms to create functional systems, such as self-assembled structures. We attempt to exploit stochasm, rather than overwhelm it, in order to create deterministic, yet highly adaptable, behavior, often by exploiting collective phenomena.

Just how much more efficient is Nature in using this approach? We can gain some insight by contrasting a modern microprocessor with a bacterium. *Escherichia coli* has a cross-sectional area of $\sim 2\ \mu m^2$, 9.2 Mbit memory (based on DNA base pairs), and the equivalent of ~1000 logic gates (*i.e.*, ~ 5 Mbit/μm^2 and ~ 500 logic gates/μm^2);[2] it solves complex information extraction problems (*e.g.*, chemotaxis) on a time scale of minutes with power consumption of 10^{-15} W, or a power density of 5×10^{-16} W/μm^2. A state-of-the-art Intel chip (*e.g.*, i5−600) has a cross section of ~ 1000 mm^2 (or $10^9\ \mu m^2$), contains 4 MB of cache memory and ~500 million logic gates (or $\sim 3 \times 10^{-8}$ Mbit/μm^2 and 0.5 logic gates/μm^2) and has a power consumption of ~100 W (or $\sim 10^{-7}$ W/μm^2). Thus, through billions of years of evolutionary development, Nature has developed a self-assembling, self-duplicating, self-healing, adaptive processing unit that has 8 orders of magnitude higher memory density and 3 orders of magnitude higher compute capacity while utilizing 8 orders of magnitude less power.

* Address correspondence to simpsonml1@ornl.gov, peter.cummings@vanderbilt.edu.

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More generally, having evolved within a noise-filled fluctuating environment (due to stochastic processes that dominate at the nanoscale), biological systems have often found strategies to make functional use of noise.[3] Examples include the control of the swimming and tumbling periods of bacteria during chemotaxis,[4] stochastically driven phenotype variability in the response to the mating pheromone in yeast,[5] and fitness-enhancing phenotypic individuality in microbial cultures.[6−8] Perhaps most intriguingly, a recent study suggests that transcriptome-wide stochasticity plays a key role in responding to environmental stresses for which evolution has not provided a specific response.[9] Since stochasticity (arising from fluctuations in composition, atomic motion, electron transport, *etc.*) increases as we probe the smaller spatial dimensions at the nanoscale, understanding Nature's approach to nanotechnology is key to us being able to create efficient, functional structures that operate in a predictable fashion with minimal energy consumption. Recent advances in theory and experiment have created the opportunity to deepen our understanding of Nature's approach to creating function within fluctuating environments. At the Center for Nanophase Materials Sciences (CNMS) at Oak Ridge National Laboratory (one of five Department of Energy, Basic Energy Sciences nanoscience user facilities), one of the three major focuses of the in-house science program is aimed specifically at this goal, drawing on CNMS-wide expertise in theory, nanobiology, and nanofabrication. In this Perspective, we outline our approach to this goal and assess the prospects for future progress.

Fluctuations at the Nanoscale—Insights from Theory. Recent advances in our theoretical understanding of the roles of fluctuations—and the closely related phenomenon of irreversibility—have provided new insight into their impact at the nanoscale. At the macroscopic scale, one way of stating the second law of thermodynamics is that, in systems subject to an applied field (such as a shear field or temperature gradient), the rate of entropy production is always positive. This is consistent with irreversibility, in that entropy production is positive independent of the sign of an applied field. However, the equations of motion that describe a system at the atomic level are completely time-reversible, suggesting that the motion can always be reversed. In the past two decades, our understanding of the way irreversibility emerges at scales between the atomic and the macroscopic—specifically, at the nanoscale—has been revolutionized by new theoretical understanding of the role of fluctuations (deviations of properties from their average value), encapsulated in the so-called fluctuation theorems (FTs). The FTs are applicable to systems *arbitrarily far* from equilibrium (see the recent review by Evans and Searles[10]). The FTs can be understood by considering Figure 1, which shows generically the probability density of $\bar{\Sigma}_t$, the time average, $\bar{\Sigma}_t = (1/t)\int_0^t \Sigma(s)ds$, of the irreversible entropy production $\Sigma(t)$. The macroscopic second law of thermodynamics implies $\bar{\Sigma}_t \geq 0$; the transient form of the FTs states that in a time-reversible ergodic system

$$\frac{p(\bar{\Sigma}_t = A)}{p(\bar{\Sigma}_t = -A)} = \exp(At) \qquad (1)$$

for any number A. Equation 1 shows that the ratio of the probability of positive entropy-producing states (PEP states, *i.e.*, those *consistent* with the macroscopic second law, shown in blue in Figure 1) to negative entropy-producing states (NEP states, *i.e.*, *violating* the macroscopic second law, shown in red in Figure 1) increases exponentially with time. The implications for the nanoscale are apparent when we recognize that (1) $\bar{\Sigma}_t$ is an extensive variable (linear in system volume), (2) $\bar{\Sigma}_t$ is proportional to the applied external field, and (3) the variance of the probability distribution is inversely proportional to system size. Hence, the *tail* of the distribution corresponding to NEP states, shown schematically in red in Figure 1, becomes larger with smaller system sizes (due to broadening of the distribution, as well as movement of the average to the left), resulting in NEP states being more persistent. The FTs were initially discovered as an anomaly in atomistic simulations, then derived using concepts of non-equilibrium statistical mechanics and nonlinear dynamical systems theory; they have since been verified experimentally in many classical and quantum systems (for an example involving the manipulation of a colloidal particle by optical tweezers, in which the time scale of second law violations can be as long as tens of seconds, see Wang *et al.*[11]). The FTs provide insight into the limits of manipulation at the nanoscale and explain counterintuitive phenomena, such as random, short-term inverse responses to applied forces. Thus, the FTs tell us that it is the *tails* of the distributions (corresponding to behavior contrary to macroscopic expectations) that can become critically important at the nanoscale.

Learning Nature's Methods To Create Function in Fluctuation-Dominated Environments. Perhaps the most complex of functions, homeostatis by a biological cell in a fluctuating and unpredictable environment (*i.e.*, the regulation of its internal environment to maintain stability and function), emerges from the interactions between perhaps 50 million molecules of a few thousand different types. Many of these molecules (*e.g.*, proteins, RNA) are produced in the stochastic processes of gene expression, and the resulting populations of these molecules are distributed across a range of values. So although homeostasis is maintained at the system (*i.e.*, cell) level, there are considerable and unavoidable fluctuations at the component (protein, RNA) level,

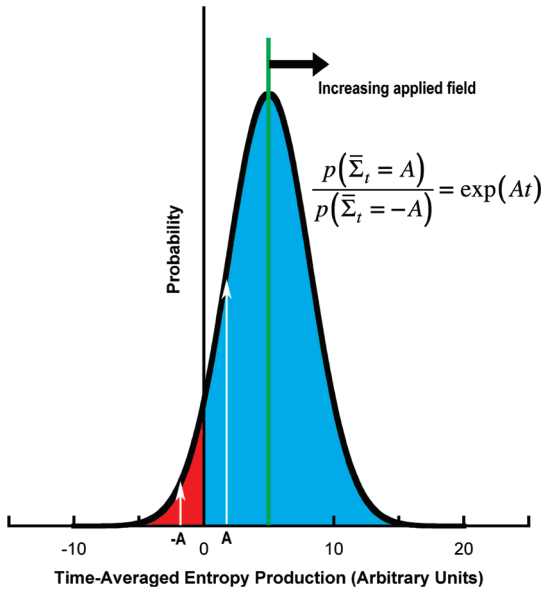

Figure 1. Schematic illustration of the probability distribution of the time-averaged irreversible entropy production $\bar{\Sigma}_t$, with positive entropy-producing (PEP) states (shown in blue) and negative entropy-producing (NEP) states (shown in red). The FTs of Evans and co-workers[10] have established the rigorous relationship between the relative probability of PEP and NEP states (see equation) as a function of system size, applied external field, and duration *t*.

and this is what cells have to teach us about the rules of composition of complex nanoscale systems. On at least some level, we understand the variability in individual components as described by the FTs, yet we have no understanding of how to integrate these fluctuating components together to achieve complex function at the system level.

> In the past two decades, our understanding of the way irreversibility emerges at scales between the atomic and the macroscopic—specifically, at the nanoscale—has been revolutionized by new theoretical understanding of the role of fluctuations, encapsulated in the so-called fluctuation theorems.

In the low-noise limit, the fluctuations in the molecular populations arise because they are synthesized discretely (*e.g.*, integer numbers of proteins) and at random times, leading to the shot noise that is well-known for semiconductor devices.[12] However, at a level more fundamental to complex nanoscale systems, fluctuations result from the sharing of limited space and limited resources. For example, 2 m of linear DNA is compacted in chromatin to fit into the cell nucleus (a volume of a few cubic micrometers), but expression requires unpacking of the chromatin, which at any one time may only happen for a limited subset of the genes. Furthermore, all genes must share a common set of finite-capacity expression machinery, so again, only a limited subset of the genes can be serviced by this machinery at any one time. As a result, a gene's expression may be uneven (*i.e.*, much noisier than shot noise; see Figure 2a), occurring episodically with bursts of relatively high activity separated by periods of no expression. The magnitude of the noise (expressed here as the variance of the noise divided by the square of the mean molecular population (CV^2)) in such episodic expression is[13]

$$CV^2 - CV^2_{\text{shot}} \propto \frac{(1 - O)}{O} \qquad (2)$$

where CV^2_{shot} is the theoretical minimum (shot-noise limited) CV^2, and O, which varies between 0 and 1, is a measure of how much of the limited shared resources are devoted to this gene (1 implies the gene receives all the resources it can use, while 0 indicates the gene receives no resources). Equation 2 points out an important trade-off (we refer to it as the "conservation of stochasticity") in biological cells that may be fundamental to all complex nanoscale systems. Stochasticity may be minimized for any individual component by distributing to this component more of the shared resources, but only at the expense of moving this stochasticity to other components, which have lost some access to these resources. An intriguing question then for both biology and synthetic complex nanoscale systems is: how should this unavoidable stochasticity be distributed across the components of the system?

In trying to formulate an answer to this question, we can consider how a cell distributes its expression capacity and therefore its stochasticity. Capacity is distributed to the genes according to regulatory mechanisms that have evolved to respond to environmental cues and thereby maintain homeostasis. Environmental signals are the biological equivalent of the external fields of the FTs, and, like Figure 1, these fields move the mean of the distribution, yet the long tails can create contrarian responses. In some cases—for example, embryonic development, which requires accurate and reliable patterns of gene expression to drive cellular differentiation in forming tissues[14]—contrarian

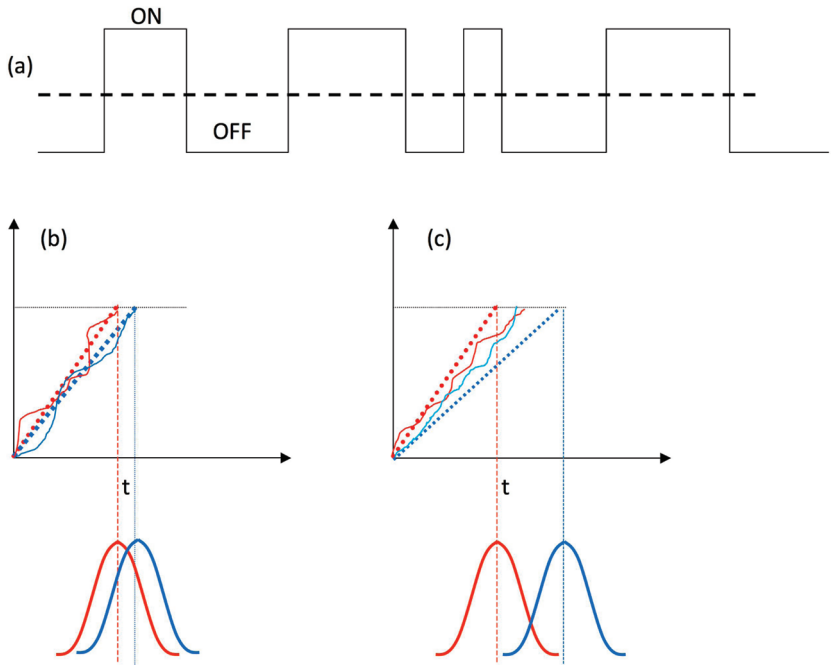

Figure 2. (a) The need to share limited space and resources leads to bursty (alternating periods of "on" and "off") and therefore very noisy gene expression. The dashed line represents the average expression level, while actual expression is always much higher or lower than average. (b) Decisions in genetic circuits may be mediated by a critical race between two molecular populations (red and blue in this figure). Although the red molecule wins the race on average, noise in both molecular populations allows the blue molecule to win in many cases as illustrated by the overlap of the distributions. (c) Environmental signal ("external fields") may change the overlap, but the long tails of the distributions still allow for rare contrarian events.

responses can be decidedly bad. So it is hardly surprising that many studies (see, for example, Fraser *et al.*[15]) have found evidence of noise minimization for some classes of genes. However, can it be inferred that the noisy genes were just those that could accept—with no harm—the unavoidable noise that must be distributed across the system?

At least in some cases, not only is noise not detrimental but instead is required for critically important functions. For example, the swimming and tumbling periods of bacteria during chemotaxis are driven by molecular noise that enables the efficient exploration of the cell's environment.[16] Genetic decision circuits (switches that choose between two disparate outcomes, *e.g.*, pathogens making a probabilistic choice between active infection or latency[17]) are especially suited to derive functional advantage from noise, by making contrarian decisions in the tails of the distributions (Figure 2b). The external fields can make these contrarian decisions rarer (Figure 2c), but these rare contrarian events may be the key ingredient in the response to a fluctuating and unpredictable environment[18] and may have an impact that is significantly out of proportion to their rarity. For example, human immunodeficiency virus-1 (HIV-1) can enter one of two developmental fates: active replication or proviral latency. Ruled by the rare events in the long tail of the noise distribution, only a small minority of infections enters proviral latency, yet these contrarian events are the main factor thwarting HIV-1 eradication from an affected individual.[19] So the tale of dealing with this nanoscale property of HIV-1 clearly lies in the tails.

As noted in the introduction, at scales from aircraft to microelectronics, engineered systems expend energy to overpower noise and create deterministic, predictable behavior. This approach will not scale to the nanoscale, and the conservation of stochasticity must be confronted: noise cannot be avoided, only shifted away from one component and onto others. However, the biological lesson is that this inherent noise cannot be wasted, as it can be a functional component with features especially useful at the nanoscale. Noise consumes no power and requires no space, yet when properly utilized can create greater function using fewer components, and it is the proper utilization of this inherent noise of the nanoscale that drives this part of the CNMS in-house research program along three pathways: (1) the study of the system-wide distribution of stochasticity, (2) the study of specific noise use strategies, and (3) the construction of synthetic nanoscale systems that may assume or mimic some of these biological features.

For the first pathway, our model system is the budding yeast, *Saccharomyces cerevisiae*, which has been sufficiently characterized at the system level so as to enable the investigation of the noise structure–function relationships sought here.[20–27] We have begun an investigation of the relationships between the deterministic and stochastic

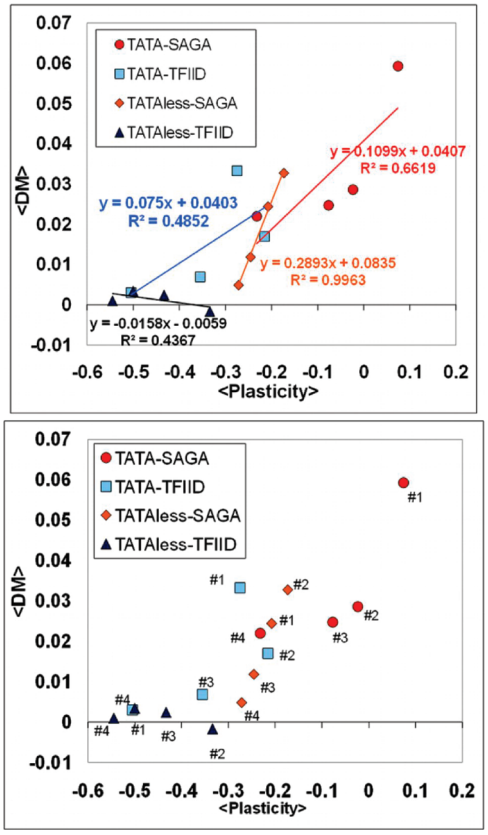

Figure 3. Plot of the noise (DM in this figure) as a function of plasticity for categories of yeast genes. Higher plasticity is strongly correlated with higher noise. Reprinted with permission from ref 28. Copyright 2010 American Institute of Physics.

components of gene expression response, and we find a direct correlation between the two types of response (Figure 3),[28] although one might have expected a large degree of plasticity (expression varying in a deterministic way in response to environmental signals) instead to be associated with low levels of random variability. This expectation would be consistent with a hypothesis where noise is used as a bet-hedging strategy when the optimal expression level is unknown. However, closer inspection indicates that our results and this bet-hedging hypothesis are not at odds. Gene expression with the largest plasticity and noise is often associated with a response to adverse environments,[29] and the plasticity in these genes implies that the optimal expression level is known, but only for stressful environments. Conversely, the stress-free environment is one with a key uncertainty: when will the next stressful environment occur? So the high noise in the expression of these genes could be an anticipatory response—the equivalent of having a fire truck make an occasional drive by a fire-prone building. A competing view holds that the noise is unimportant and is instead just an acceptable side effect of the more important feature of plasticity.[30] Discerning between these two competing hypotheses requires closer examination of how noise is used in individual gene circuits.

> Noise consumes no power and requires no space, yet when properly utilized can create greater function using fewer components.

One could hypothesize that, in physical systems, the tail of the distribution in many properties provides a bet-hedging strategy to optimize the *dynamic* response of the system. For example, in the presence of an applied magnetic field, the distribution of magnetic moments of the domains or spins will include a nonzero population of spins that have an opposite (contrarian) orientation to the applied field. Upon reversing the applied field, the reversal of the majority of the spins will be seeded heterogeneously by the small set of previously contrarian spins. If such contrarian domains or spins did not exist, the response to the change in direction of the applied field would proceed by a much slower homogeneous nucleation process, initiated by fluctuations. Likewise, quite generally, the maintenance of NEP states in a system under an applied field (such as shear) could be interpreted as providing the states/domains that would nucleate a response to a reversal of the applied field.

For the second pathway—specific mechanisms of the use of noise to provide more function in less space—we focus on viral gene circuits. Viruses, in general, are important in nanoscience as they are programmable nanoscale machines that have been harnessed for controlled synthesis and directed assembly of nanomaterials.[31−34] For our purposes, retroviruses are of particular interest as they perform complex tasks with a very limited set of components; that is, these are ideal model systems for understanding how fluctuations may be used to get more function in less space. Working with collaborators in the Weinberger laboratory (University of California, San Diego), we used noise spectroscopy to elucidate some aspects of the molecular positive feedback mechanism that initiates the cascade of events that leads either to latency or active

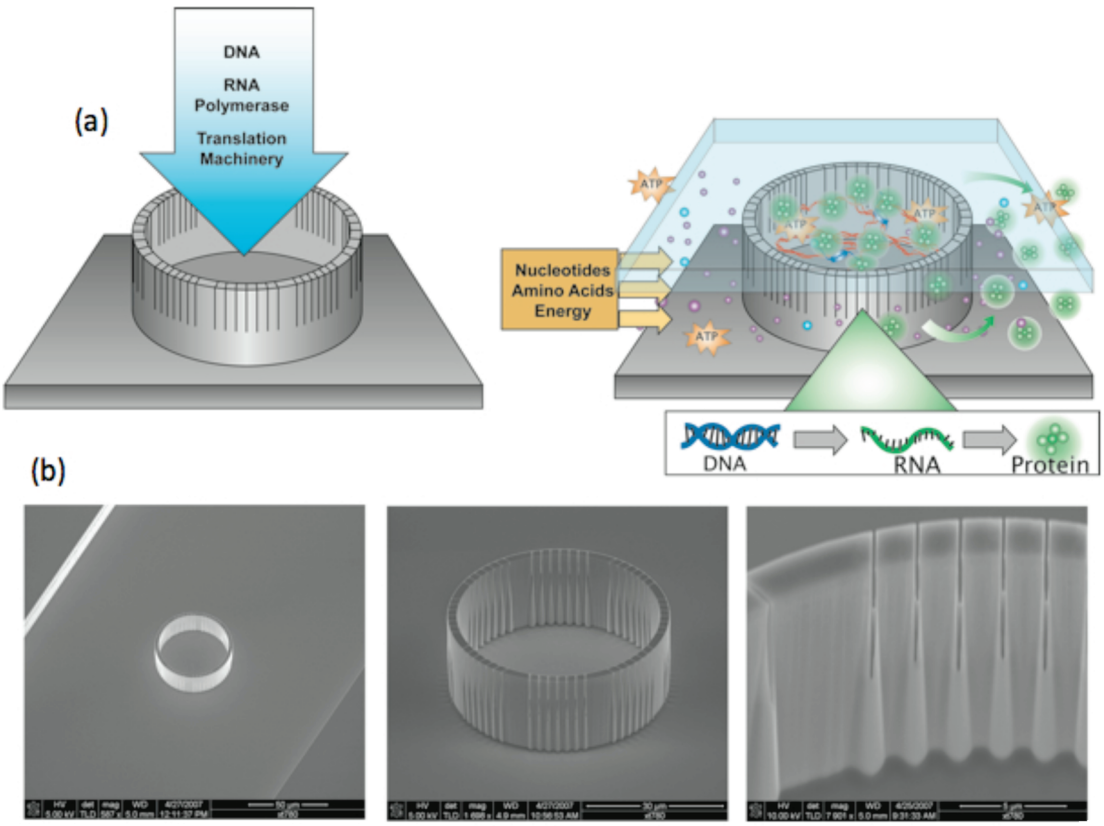

Figure 4. (a) Cell mimic concept that includes a microscale enclosure with nanoscale features placed within a microfluidic environment. The cell mimic structure is loaded with transcriptional and translational machinery and sealed. The transcriptional and translational machinery is contained within the cell mimic structure while small molecules may travel through the pores to sustain the function of the mimic device. (b) Micrographs of fabricated cell mimic structures showing placement within a microfluidic channel (left), the cell mimic structure (middle), and the nanoscale pores (right).

replication of HIV-1.[17,35] The HIV-1 circuit that mediates the decision between active infection and latency is a genetic decision circuit subject to the contrarian effects enabled by noise[36−38] (Figure 2), and this circuit is known to have high noise[35] that is further enhanced by positive feedback.[17] Uncovering the details of how noise is used to drive function in viral systems seems a promising approach for understanding how to design these strategies into synthetic nanoscale systems.

Finally, the third pathway aims to close the loop between biological lessons and synthetic complex nanoscale systems. We contend that the tools of nanoscience provide an opportunity to create synthetic systems that match the biological scale, and as these abiotic systems approach biological functional density, they can begin to assume some cell-like characteristics.[39] We have used the fabrication capabilities at the CNMS for the development and routine application of small-volume reaction containers with defined nanometer-scale pores[40] that are important steps along the path to cell-free model systems (Figure 4). The combination of these techniques with conventional deposition and lithography procedures enables the production of test structures that span the nanometer to centimeter length scales[41] (Figure 4b). We have shown that molecular transport, parallel to the plane of the substrate, can be precisely defined by physical and chemical definition of the pore structure.[40,42−44] Presently, pore structures on the order of a few nanometers can be routinely created (Figure 4b, right).[41] We have filled these membrane structures using various liquid deposition technologies and enclosed them with a soft polymer lid structure to enable the testing of small (picoliter scale) reaction volumes with controlled reagent exchange. These "cell mimics" have been filled with proteins, or with DNA molecules of desired gene sequence, and combined with transcription and translation machinery to produce the corresponding protein(s) for as many as 24 h, which is well beyond what is typically observed in static, conventional scale structures (microliter volume in microcentrifuge tubes). A long-term goal of this work is to construct abiotic systems that test, perhaps even advance, the function−structure relationships elucidated by work with the first two model systems.

CONCLUSIONS

The nanoscale is an environment in which fluctuations dominate, and our ability to apply external forces in a deterministic fashion is limited.

Nature's approach to nanotechnology is to embrace and to exploit fluctuations and noise to create adaptable, persistent, optimized functional architectures. Part of Nature's flexibility is achieved by distributing the overall unavoidable noise into parts of the system where it is at least harmless, and at best advantageous. By striving to understand Nature's design paradigms, we hope to create physical nanosystems that likewise distribute noise, as Nature does, in an optimal fashion.

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