# Rockets, gauges, and pendulums: applying engineering principles to cell biology

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**ABSTRACT** **From flight to radar to Velcro, biological form and function have inspired engineers for centuries. It is equally valuable to consider whether concepts in engineering might provide insights into core biological processes. To explore this idea, cell cycle checkpoints, biological clocks, and signaling pathways are viewed here from an engineering perspective. Engineering concepts covered include gauge error, the distinction between precision and accuracy, and the Taguchi method of robust design. Also discussed is the Pareto principle, which describes the observation that, in complex systems, a minority of the components (or inputs) are responsible for a majority of the outputs. These concepts enable engineers to manage complexity, both in system design and in operation. Thus, with new techniques and large data sets revealing ever-increasing levels of biological complexity, an engineering mindset may be particularly valuable for the study of living systems.**

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On 20 February 1962, astronaut John Glenn, the commander of the *Friendship 7* space capsule, was preparing for reentry into the atmosphere and the successful completion of the first manned orbit mission of the United States' fledgling space program. However, all was not well; a warning light indicated that the heat shields might have come loose, due to improper deployment of a rubberized impact bag (Kranz, 2009). Even slight defects in the alignment of the heat shields would result in incineration of the capsule upon reentry. To compensate, engineers at mission control debated the viability of leaving the rocket boosters positioned in the center of the heat shields during reentry in order to maintain their proper position. These rocket boosters were designed to slow the craft as gravity pulled it earthward. A critical question was whether leaving the boosters attached would severely disrupt flight dynamics during reentry. Meanwhile, Christopher Kraft, NASA's lead engineer, suspected that the real problem was that the monitoring system had inappropriately activated the warning light, especially as his engineering team had concluded that a mechanical failure of the bag deployment was highly unlikely. John Glenn successfully touched down in the Atlantic, and later analysis of the capsule revealed that the heat shields were, indeed, properly positioned. Kraft had correctly concluded that the defect was more likely an errant gauge rather than a core component of the spacecraft.

Reading this account recently, I came to wonder whether concepts and principles used in engineering might apply to living systems. Clearly, the converse is true: for centuries engineers have turned to nature for insight. Moreover, seeking design inspiration from nature is currently enjoying a renaissance. The Wyss Institute at Harvard launched a program devoted to Biologically Inspired Engineering (https://wyss.harvard.edu/). Current projects include ambulatory microrobots (insect-inspired), surgical glue (slug-inspired), ultrarepellant surfaces (pitcher plant–inspired), biodegradable plastic (shrimp shell–derived), and swimming–diving robots (diving beetle–inspired). I am convinced that it is equally valuable for biologists to explore whether key concepts in engineering might provide insights—or at least a different perspective—into core processes in cell and developmental biology.

## THE GAUGE IS OFTEN LESS ACURATE THAN THE PROCESS BEING MONITORED

Many of us have driven cars blithely ignoring the red warning lights on the dash. Experience has taught us that, like the situation with the heat shields of *Friendship 7*, the car is probably working fine and the problem lies with the gauge. Automobile fuel indicators are

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notorious for being inaccurate. While modern fuel gauges accurately measure the volume units of fuel injected into the manifold, this does not account for variability in fuel quality and density changes with temperature. Dashboard tire-pressure gauges installed on newer automobiles are especially vulnerable to the latter; hence the frequent activation of low-pressure warning lights on cold days. Do these flaws in gauges and monitoring systems apply to biological processes? Perhaps the well-studied cellular "gauges" are also less accurate than the biological processes being monitored?

Cell cycle checkpoints provide an excellent system to explore this issue. For example, in response to incomplete or improper microtubule/kinetochore attachments, spindle-assembly checkpoints prevent entry into anaphase, providing time for error correction. A great deal is known about the molecular composition of the "gauges" located at the kinetochore monitoring proper microtubule/kinetochore attachment (Salmon and Bloom, 2017). The spindle-assembly checkpoint is extremely sensitive, and microtubule attachment failure at a single kinetochore results in checkpoint activation (Rieder *et al.*, 1995). An unavoidable consequence of this exquisite sensitivity may be inappropriate activation of the spindle-assembly checkpoint. That is, even though all of the kinetochores have formed proper connections with microtubules, the spindle checkpoint signals that an error has occurred, arresting the cell in metaphase (Figure 1). Like the warning light on *Friendship 7*, in some instances the metaphase arrest may be a result of improper activation of the spindle checkpoint, rather than defects in spindle assembly.

Experimentally testing the idea that the set point of the spindle-assembly checkpoint is such that it activates inappropriately is difficult, because demonstrating correct microtubule/kinetochore association and tension at the molecular level on all chromosomes is not feasible. However, if one assumes that the error rate at which the spindle-assembly checkpoint is improperly activated is higher than that for the process it is monitoring (microtubule/kinetochore attachment), this provides an alternative perspective on the phenomenon known as checkpoint adaptation. This refers to the well-documented phenomenon in which cells eventually override a checkpoint-induced delay even if the error has not been corrected (Toczyski *et al.*, 1997). For example, in cells in which the spindle assembly checkpoint is activated, mitotic arrest can be maintained for hours (Uetake and Sluder, 2007). However, the cells are eventually released from the metaphase arrest even though kinetochore/microtubule association defects are still present. This phenomenon of checkpoint adaptation is also referred to as mitotic slippage (Huang *et al.*, 2010). Elegant recent work demonstrates that the slippage occurs in spite of the fact that the checkpoint remains fully active (Bonaiuti *et al.*, 2018).

Why mitotic slippage occurs is not fully understood, but it is generally viewed as a deleterious event or a means of activating apoptotic pathways eliminating the offending cell (Tao *et al.*, 2005). An alternative view of the functional significance of adaptation is that it provides a mechanism for the cell to compensate for the hair-trigger sensitivity of many cell-cycle checkpoints. Like the gauge on Glenn's spacecraft, in many instances the checkpoint may be inappropriately activated. This suggests that adaptation may have evolved as a means of allowing these normal cells to divide in spite of an active checkpoint. Thus, while checkpoint-induced delays provide time for correction and completion of key events in the cell cycle, the adaptation-induced override rescues inappropriately arrested normal cells. Cell-cycle checkpoints monitor numerous other processes, such as DNA replication. It may be that these checkpoints are also more error-prone than the cellular processes being monitored, and checkpoint adaptation has evolved to compensate.

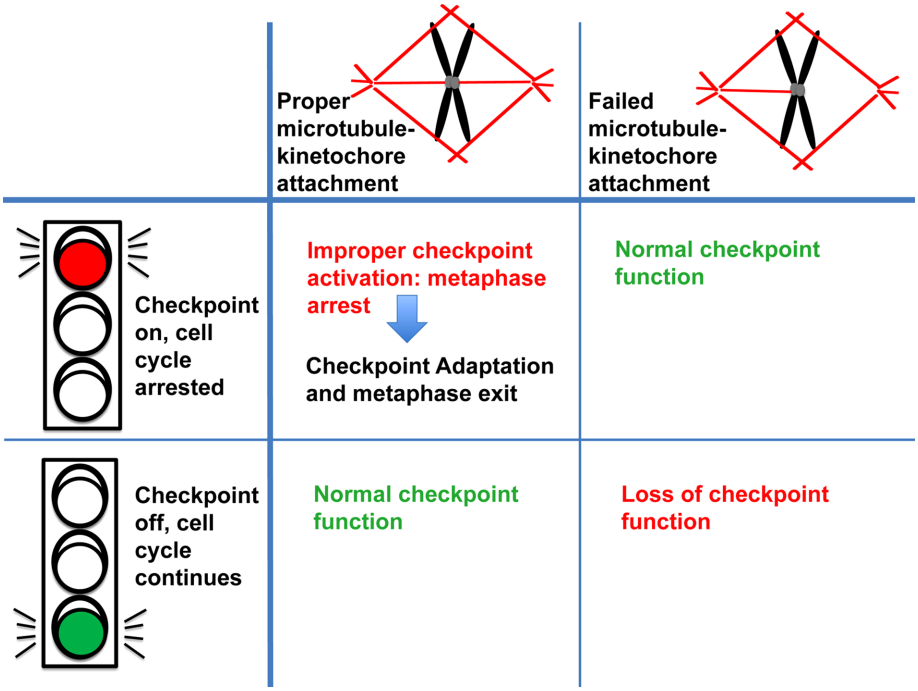
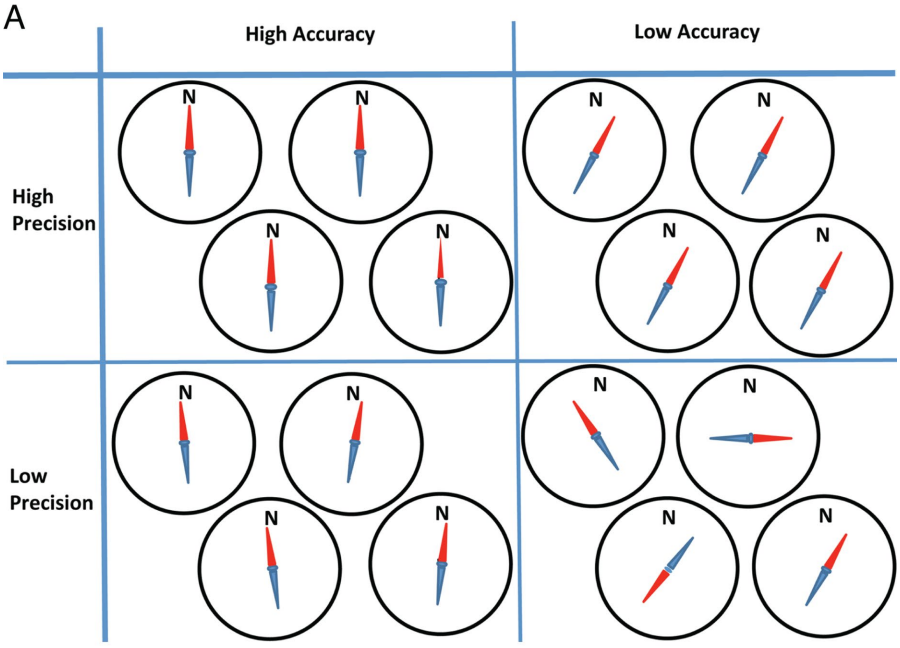



**FIGURE 1:** Gauge error. In engineering, there are numerous examples in which gauges and monitoring systems are less accurate than the process being monitored. This may be true for cell-cycle checkpoints and readily explains checkpoint adaptation, the phenomenon in which cells eventually progress through a checkpoint-induced arrest. As shown, the spindle assembly checkpoint may be activated and arrest cells in metaphase with some frequency even though spindle formation is normal. Adaptation rescues these cells by overriding the checkpoint-induced arrest.

## PRECISION VERSUS ACCURACY

Most biologists would be hard pressed to define the difference between the terms *precision* and *accuracy*. Consequently, with a few exceptions, they tend to be used loosely and interchangeably in the biomedical literature. In contrast, these terms have distinct and very specific meanings in the engineering realm. Accuracy refers to how closely a measured value matches its true value. Precision refers to how close repeatedly measured values are to one another. For example, a compass is precise and accurate if, in five independent readings, the needle points to north (0°). If all five readings point to the same reading to the northwest (270°), the compass is precise but not accurate. Alternatively, if there is scatter in the five readings (354°, 357°, 0°, 2°, 4°), but they are centered around north, the compass is accurate but not precise. If the five readings are randomly distributed about all points on the compass, it is neither accurate nor precise (Figure 2A).

It would be beneficial for biologists to follow the lead of engineers and include the distinction between precision and accuracy



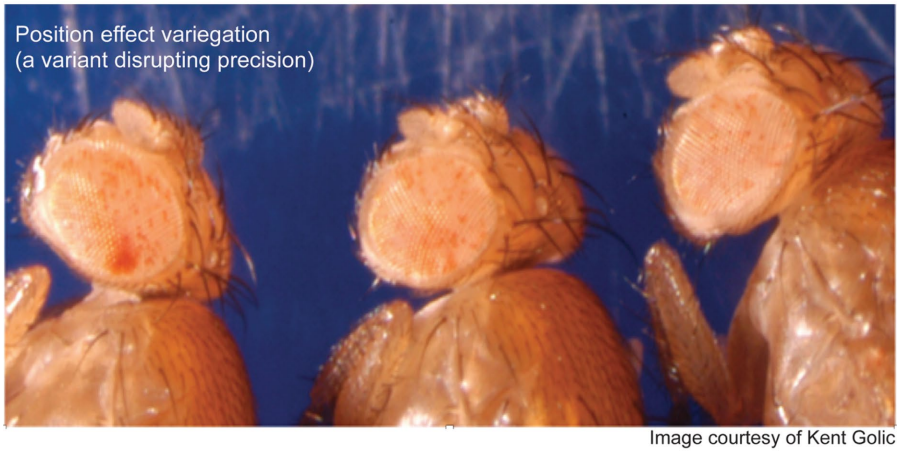
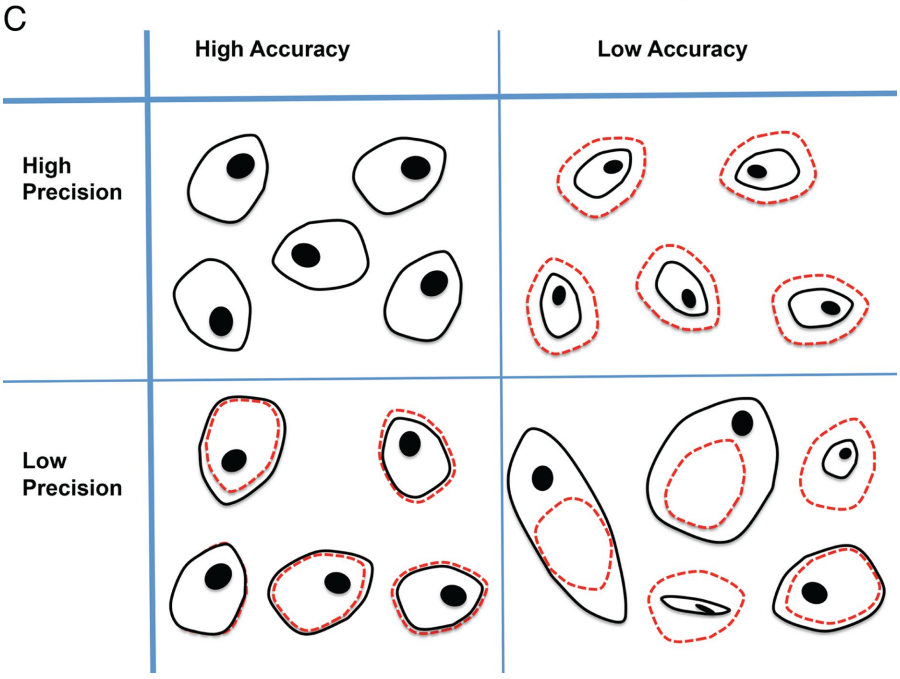




Image courtesy of Kent Golic




in their experimental design and analysis. This is especially true for the genetic analysis of cellular and developmental processes. In performing genetic screens, there is a strong bias to select for mutants that disrupt accuracy but maintain precision.

Whether it is the number of segments in a fly embryo or flower color, geneticists are drawn to mutants that produce a constant, rather than a variable, change in a specific trait. Scanning the extensive lists of mutants for each model organism drives this point home: the vast majority of variants produce altered, but consistent and reproducible phenotypes. Pattern-seeking is an innate human trait, and social scientists speculate that it drives much of human behavior (Ackerman, 2004). Thus, it is natural, perhaps even inevitable, that geneticists would focus on variants with consistent pleasing patterns.

While focusing on this class of mutations has been extremely productive, we should not be so quick to toss out variants that disrupt precision. McClintock's discovery of transposable elements in maize was due to her focus on mutants that produced bewildering sectoring patterns that varied from kernel to kernel (McClintock, 1950). Similarly, we have learned a great deal about chromatin structure and gene regulation from the study of chromosome rearrangements in *Drosophila* that produced variegated eye-color patterns, a phenomenon referred to as position-effect variegation (Elgin and Reuter, 2013; Figure 2B). These successes should motivate geneticists to pay more attention to mutations that disrupt the precision of a specific trait. For example, studies of the control of cell size have been notoriously difficult, because size is influenced by autonomous and nonautonomous factors (Ginzberg *et al.*, 2015). In addition, duration, as well as the rate of cell growth, influences cell size (Lucena *et al.*, 2018). While numerous mutations that disrupt cell

**FIGURE 2:** Precision versus accuracy. (A) In the field of engineering, these terms have precise and distinct meanings. As shown, a compass can be extremely precise, but inaccurate. It would be useful for cell biologists to determine whether perturbations in cellular processes are the result of defects in precision or accuracy. (B) For example, key epigenetic factors were discovered by focusing on gene rearrangements that caused position-effect variegation, a phenomenon that disrupts precision of the red-eye phenotype. (C) Additional insight into cell-size control may come from focusing on mutations that disrupt precision of this phenotype (red dotted lines indicate normal cell size).

size have been identified (Fantes, 1981; Stocker and Hafen, 2000), little effort has been devoted to determining whether they disrupt precision or accuracy of cell size control. Mutations in the former class, disrupting the precision of cell size control, are likely to be especially informative, as this would be the phenotype of the mutants with disrupted key factors that the cell uses to determine size (the "measuring stick" of the cell; Figure 2C). In an analogy with the compass, if the needle always incorrectly points northwest instead of north (precise but not accurate), key aspects of the compass are still functional. But if the needle points in random directions, core mechanisms of the compass are likely disrupted.

## BIOLOGICAL ROBUSTNESS AND THE TAGUCHI METHOD

The past two decades have brought a wealth of knowledge regarding the components and pathways controlling key cellular events. This has facilitated analysis of the logic and regulatory features of these pathways and given rise to the concept of biological robustness. Robustness refers to the property that cells and tissues function normally regardless of variations in their internal and external environment. A number of homeostatic mechanisms responsible for robustness have been characterized. These include biochemical feedback, feedforward mechanisms, parallel pathways, and substrate inhibition mechanisms (Nijhout *et al.*, 2017). A shared feature of these mechanisms is that the increase in robustness is achieved through additional elements superimposed on the core process. This would be analogous to adding an extra layer of insulation to an incubator.

Another means of increasing robustness is modifying the properties of the core components of the process such that they are insensitive to environmental perturbations. The latter method is often used in engineering design. An example of these alternative approaches toward achieving robustness comes from the development of accurate pendulum clocks. In the first generation of these clocks, temperature changes compromised the accuracy of the clocks, because the length of the pendulum (the swinging arm) changed with changing temperature. To compensate, glass vials of mercury were attached to the bottom of the pendulum. The expansion and contraction of the mercury altered the pendulum's center of gravity, compensating for the changes in pendulum length (Graham, 1727). While this addition improved accuracy, it was an imperfect solution, because the temperature-induced expansion/contraction rates of the mercury and pendulum arm differed. Dramatic increases in accuracy were eventually achieved by developing pendulum arms made of quartz, a material that does not change volume with temperature (Matthys, 2004). In this instance, robustness was achieved by selecting materials that reduce variation rather than by the addition of compensating elements.

In manufacturing, building robustness into the initial stages of the design is known as the Taguchi method, named after the Japanese engineer who pioneered the concept (Roy, 2010). His goal was to identify design parameters that reduced variation without eliminating the causes of the variation. Taguchi developed techniques to find values for component parts that minimized the impact of uncontrollable sources of variation, such as temperature and humidity. For example, one might want to design an irrigation pipe that is stiff but has some degree of flexibility. Because the pipes will be exposed to varying temperatures, the Taguchi method directs the designer to test the range of flexibility of different materials and thickness as temperature varies. In the hypothetical example shown in Figure 3A, constructing the 3 mm–thick pipe with fiberglass rather than plastic produces a more

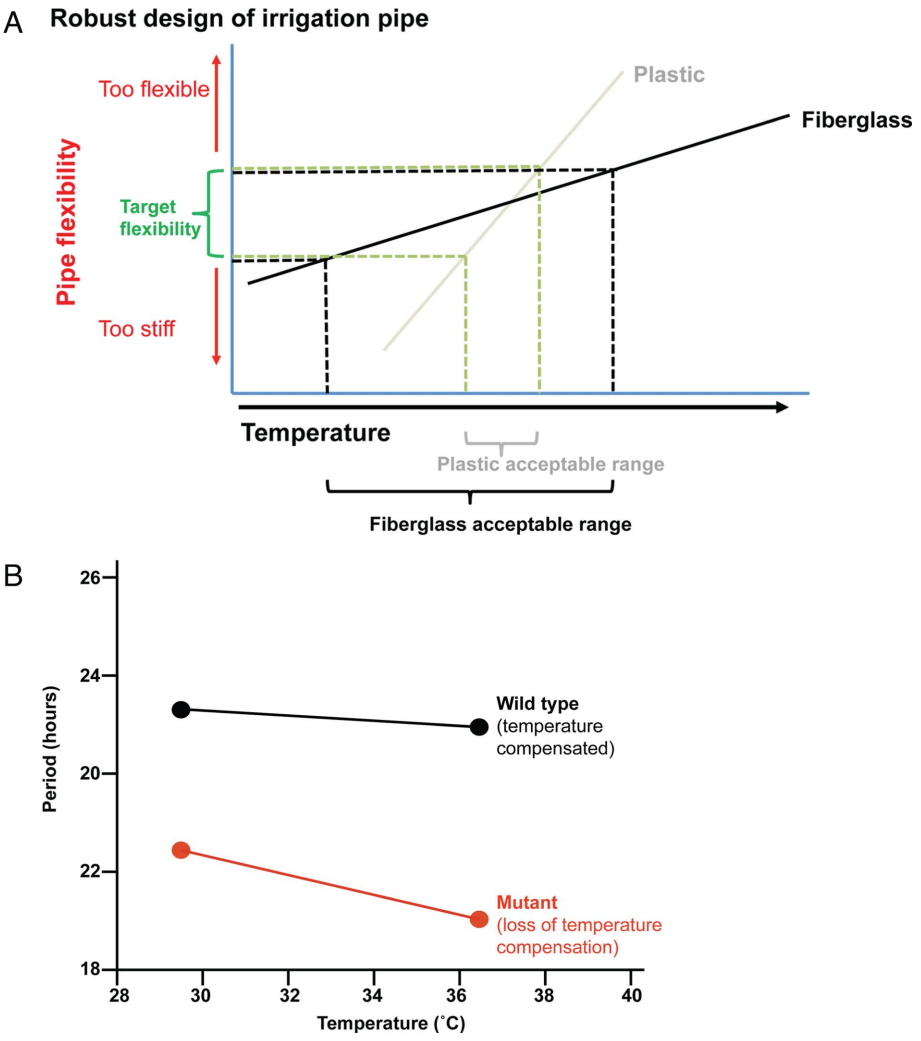



FIGURE 3: (A) The Taguchi method of robust engineering identifies components and parameters early in the design process that minimize the impact of uncontrollable sources of variation, such as temperature and humidity. In this hypothetical example, using fiberglass, rather than plastic, proves to result in a more robust design with respect to optimal flexibility over a broad temperature range. (B) Temperature-compensated circadian clocks provide evidence for the influence of Taguchi-like principles of robustness during cellular evolution. Temperature compensation is achieved through the properties of sequences embedded within the core PER clock protein rather than through additional external regulating elements. As temperature increases, the protein has a lower affinity to a CKI-ATP that targets PER and a slower release of the product of the reaction, CKI-ADP. Mutations in these regions result in the loss of temperature compensation.

robust design because of the lower variation of fiberglass in flexibility with changing temperature.

Is there evidence that forces analogous to Taguchi's robust design principles drive cellular evolution? A promising place to look is biological clocks, because, unlike many other cellular processes, they do not vary with temperature. For example, while many enzymatic reaction rates double with each 10°C increase in temperature, the circadian period varies little over a broad range of temperatures (Segel, 1975). As in early pendulums with a vial of mercury attached, one might imagine that temperature compensation is achieved through feedback mechanisms superimposed on the enzymatic machinery of the clock. However, recent work demonstrates that Taguchi-like principles are in play. The authors demonstrate that sequences embedded within the PER core clock protein complex endow it with insensitivity to temperature (Shinohara *et al.*, 2017; Figure 3B). As temperature increases, the protein has a lower affinity to a CKI-ATP that targets PER and slows release of the product of the reaction, CKI-ADP. In addition, when these protein domains are transferred to another protein targeted by these kinases, it confers a similar temperature compensation. Much as with the quartz pendulum arm, early in the evolution of the biological clock, temperature compensation was directly built into the components driving the clock.

The degree to which biological robustness is achieved through properties intrinsic to the components driving the process is unknown. Demonstrating that Taguchi-like principles of robustness are operating in living systems requires detailed knowledge of the core machinery driving the process and careful biochemical studies similar to those performed for the PER clock complex. With time, my bet is that many more examples will be forthcoming.

## THE PARETO PRINCIPLE BRINGS GOOD NEWS TO CELL BIOLOGISTS

New technologies and large data sets have yielded many insights, but also highlight the complexity of cellular processes. This is most evident in the study of cell signaling pathways. Studies focusing on the regulation of signaling pathways reveal multiple and daunting levels of complexity. For example, genomic and proteomic studies of the Notch signaling pathways yield hundreds of proteins that influence Notch signaling, from transcription factors to regulators of splicing and the proteasome (Guruharsha *et al.*, 2012). The resulting interaction diagrams look strikingly similar and as complex as airline flight route maps. These maps are useful for identifying interaction nodes, but the functional significance of the majority of interactions remains unknown.

The Pareto principle provides a strategy for analyzing complexity (Iqbal and Rizwan, 2009). Pareto, a nineteenth-century Italian philosopher, realized that 80% of Italy's wealth was concentrated in 20% of its population. Following up on this observation, Pareto discovered that highly skewed distributions were the rule, rather than the exception, for which he developed the axiom known as the Pareto principle—80% of the effect (output) is derived from 20% of the causes (input). For example, he found that, in Italy, 80% of the production came from 20% of the companies. The distribution is not necessarily 80/20 but many distributions approximate this ratio: for example, the top 20% of professional golfers earn 68% of the prize money. Engineers rely on the Pareto principle for equipment maintenance. For complex equipment, the majority of the errors/breakdowns originate from a minority of the parts. A Department of Defense analysis revealed that three parts (the oil valve, oil pump, and exhaust valve) accounted for 70% of marine diesel engine failures (Banks *et al.*, 2001). This information is valuable for determining which spare parts to carry on a voyage.

The Pareto principle provides a strategy for coping with the staggering complexity of the cellular machines and processes. For example, while the Notch interactome clearly identifies key interaction hubs, the maps do not provide information concerning the strength of the inputs and outputs (Guruharsha *et al.*, 2012). It is highly likely that the Pareto principle applies to biological systems, and only a small subset of inputs into the Notch signaling interactome hub are responsible for the majority of outputs. Similarly, the spliceosome is one of the most complex enzymatic machines in the cell. Numerous studies have examined mutants and other causes of splicing defects (Wang and Lee, 2018). It is likely that, as in diesel engines, the majority of defects arise from a small number of components. Both in the Notch pathway and in the spliceosome, identifying and focusing on these key inputs and components would be a productive line of research.

On a final note, it is a good bet that the Pareto principle also applies to our own laboratory research activities. That is, 20% of our effort in the lab is probably responsible for the majority of our output. The trick then is to identify that all-important 20%.

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