**Text of practice exercises for Module 1.6**

Anti-inflammatory drugs may be protective for the occurrence of Alzheimer’s Disease.

Clinical seizures have been estimated to occur in 0.5% to 2.3% of the neonatal population.

Ultimately p53 guards not only against malignant transformation but also plays a role in developmental processes as diverse as aging, differentiation, and fertility.

Injuries to the brain and spinal cord have long been known to be among the most devastating and expensive of all injuries to treat medically.

An IQ test measures an individual’s abilities to perform functions that usually fall in the domains of verbal communication, reasoning, and performance on tasks that represent motor and spatial capabilities.

As we can see from Figure 2, if the return kinetic energy is less than 3.2 Up, there will be two electron trajectories associated with this kinetic energy.

**Text for editing, demo edit 1, Module 1.7 (optional)**

Immortality is an alluring concept. Some scientists believe that it will be possible to "upload" one's mind by recreating the circuitry of the brain in silico. Before we can upload brains, we first must reverse-engineer neural circuitry and begin by creating a circuit map.

Electron microscopy provides the only possible method through which we're able to clearly visualize synapses and follow neural processes. Volumetric reconstruction of neural tissue using electron microscopic resolution is necessary to map neural circuitry. Focused ion-beam scanning electron microscopy (Knott et al. 2008) gives excellent quality images, but fails to process tissue pieces larger than 40 microns in diameter. Thin sections imaged with transmission electron microscopy succumb to the damaging effects of manual handling and section distortion. Thus, it's most prudent to use a method that images the block-face directly and is capable of imaging large block-faces. Serial block-face scanning electron microscopy (SBEM; Denk and Horstmann 2004) provides both necessary components.

Using SBEM, Dr. Kevin Briggman and associates (Briggman, Helmstaedter, and Denk 2011) recently mapped the connections between starburst amacrine cells and bipolar ganglion cells in the mouse retina to better understand the wiring specificity, elucidating the cellular circuit between starburst amacrine cells and direction-selective bipolar retinal ganglion cells.

By staining a 200-micron piece of retina, which contained the entire arborization field of a starburst amacrine cell with an extracellular stain that could outline cells and neural processes in SBEM, Briggman was then able to reconstruct neural processes. Based on morphology, he assessed the locations and sizes of putative synapses on these processes.

Unfortunately, synapses were invisible within the data because the tissue was only stained with an extracellular, electron-dense stain and some synaptic features are intracellular. In an effort to address this ambiguity, Briggman then stained a second piece of tissue where synapse-associated features were stained and visible. He then correlated the extracellular morphology found at synapses between the first and second pieces of tissue.

This is the first example of relatively large neural circuit reconstruction and it solved controversy about exactly how starburst amacrine cells are wired to be directionally-selective. The next steps in whole-brain circuit reconstruction will be large sample preparation (Mikula, Binding, and Denk 2012) and imaging on a whole-brain SBEM for mapping the whole mouse brain as a first mammalian complete connectome (Seung 2011).

Text of practice exercise (for editing) Module 2.3

A recommendation was made by the DSMB committee that the study be halted.

Major differences in the reaction times of the two study subjects were found.

It was concluded by the editors that the data had been falsified by the authors.

The first visible-light snapshot of a planet circling another star has been taken by NASA’s Hubble Space Telescope.

Therefore, the hypothesis that the overall kinetics of a double transtibial amputee athlete and an able-bodied sprinter at the same level of performance are not different was rejected.

**Text of practice exercises Module 2.5**

The fear expressed by some teachers that students would not learn statistics well if they were permitted to use canned computer programs has not been realized in our experience. A careful monitoring of achievement levels before and after the introduction of computers in the teaching of our course revealed no appreciable change in students’ performances.

Review of each center’s progress in recruitment is important to ensure that the cost involved in maintaining each center’s participation is worthwhile.

It should be emphasized that these proportions generally are not the result of significant increases in moderate and severe injuries, but in many instances reflect mildly injured persons not being seen at a hospital.

Important studies to examine the descriptive epidemiology of autism, including the prevalence and changes in the characteristics of the population over time, have begun.

There are multiple other mechanisms that are important, but most of them are suspected to only have a small impact or are only important because of impact on one of the three primary mechanisms.

After rejecting paths with poor signal-to-noise ratios, we were left with 678 velocity measurements of waves with 7.5 seconds period and 891 measurements of 15 second waves.

It is suspected that the importance of temperature has more to do with impacting rates of other reactions than being a mechanism of disinfection itself since ponds are rarely hot enough for temperature alone to cause disinfection.

It was assumed that due to reduced work at the joints of the lower limbs and less energy loss in the prosthetic leg, running with the dedicated prostheses allows for maximum sprinting at lower metabolic costs than in the healthy ankle joint complex.

**Text for editing, demo edit 2, Module 2.8 (optional)**

Scientists are still looking for small size smart robots that can navigate in dynamic and unknown environments. This challenge inspired Tahmid Latif and Alper Bozkurt from North Carolina State University to use cockroaches as biobots (biological robots). They developed a wireless biological interface that uses an electronic interface to remotely steer cockroaches. This concept helps to create a mobile web of sensors that uses cockroaches to collect and transmit data, such as locating survivors in hard areas during earthquakes.

Cockroaches have antennas -called cerci- to sense: tactile, temperature and humidity. Researchers used these antennas to drive the cockroach by sending a series of electrical pulses to it. The system consists of: a microprocessor with Zigbee interface [1], electrodes and a battery. The user controls the microprocessor wirelessly using a Zigbee transceiver; the microprocessor sends electrical pulses to the cockroach’s antennas using electrodes and then the cockroach moves.

Tahmid Latif and Alper Bozkurt used Madagascar Hissing cockroach during their analysis because of: its larger size (~50-75mm), slow speed (~3cm/s), long life span (~2 years) and robustness. Before the experiment starts, they anesthetized the cockroach by cold-treatment (4C) for 45-60 minutes. They attached one side of the electrodes (5cm long stainless steel coated with 250um thick Teflon) to the antennas to serve as electronic reins, injecting small charges into the roach’s neural tissue. The charges trick the roach into thinking that the antennas are in contact with a physical barrier, which effectively steers them in the opposite direction. The researchers evaluated two microprocessors that control the electrodes: Microchip's PIC16F630 [2] and Texas Instrument’s CC2530 [3]. CC2530 was better because of its low weight (500mg), Zigbee module connectivity and the availability of 21 general purpose I/O. CC2530 gets its power from the 90mAh Li-Po battery.

Cockroaches followed an S-shaped trajectory drawn on the laboratory floor and spent 81 sec. with 10% success rate to complete the route. This finding opens the door to scientists to start using insects in biobots world but the system's overall weight is still a concern in this new field and needs more studies to reduce its size.

**Text for editing Module 3.2**

Scientists are still looking for small size smart robots that can navigate in dynamic and unknown environments. This challenge inspired Tahmid Latif and Alper Bozkurt from North Carolina State University to use cockroaches as biobots (biological robots). They developed a wireless biological interface that uses an electronic interface to remotely steer cockroaches. This concept helps to create a mobile web of sensors that uses cockroaches to collect and transmit data, such as locating survivors in hard areas during earthquakes.

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**Example paragraph 1 Module 3.5**

Most scents remain constant in their quality over orders of magnitude of concentration (12). Nevertheless, at high concentrations, quality tends to be negatively correlated with intensity, as was the case, for example, for the cinnamon oil used in this study. Hence, reliability of absolute scorings was achieved by calibrating the amount of perfume ingredients with initial ratings for intensity against a reference substance of known concentration. The final concentrations were in principalchosen in a way such that individual ratings showed variance among participants within the sliding scale between 0 and 10 (meaning that people could decide whether they liked a scent or not). This procedure seemed successful for most scents; however, the concentrations for bergamot (highest average ratings) and vetiver (lowest average rating) could probably been reduced even more, as both scents did not show any discriminating power at the level of common alleles (people agreed largely on the quality of these two scents) (see Table 2). Interestingly, the pooled rare alleles showed discriminating power for… (Word count: 212)

**Example paragraph 2 Module 3.6**

Although the methodological approaches are similar, the questions posed in classic epidemiology and clinical epidemiology are different. In classic epidemiology, epidemiologists pose a question about the etiology of a disease in a population of people. Causal associations are important to identify because, if the causal factor identified can be manipulated or modified, prevention of disease is possible. On the other hand, in clinical epidemiology, clinicians pose a question about the prognosis of a disease in a population of patients. Prognosis can be regarded as a set of outcomes and their associated probabilities following the occurrence of some defining event or diagnosis that can be a symptom, sign, test result or disease.

**Text for editing, demo edit 3, Module 3.10 (optional)**

Traditional methods for controlling biological signals in cells are a sledgehammer: they are global, slow, and often non-specific. The authors of this paper describe their new technique to generate local, fast, and targeted cell signaling in live cells that are genetically altered to have light-sensitive proteins. They engineered a cellular perturbation system applicable to many signaling proteins. The main requirement for the candidate signaling protein is to be naturally activated by interactions that re-localize it to the membrane.

Levskaya et al. built this membrane recruitment system using photosensitive proteins named Phytochromes. These proteins from plants detect red and near-infrared light through the photoisomerization of a bound chromophore. This light detection changes the Phytochrome’s conformation between a state under red light that binds directly to a phytochrome interacting factor (PIF) and a state under infrared light that doesn’t bind to PIF. The scientist added a membrane-localization part to the Phytochrome, and attached a signaling protein to the PIF to complete their system. A cell illuminated with infrared light under the microscope will have inactive, free-floating, PIF-attached signaling proteins. When the scientist points a red laser in the phytochrome-rich membrane, the PIF-attached proteins are forced to stay close to the membrane; effectively increasing the activity of the signaling proteins. Turning off the red laser frees the proteins and turns off the cellular signal.

To demonstrate the feasibility of this new technique they focused on the signaling proteins Tiam and intersectin, precursors of the Rho-GTPases Rac1 and Cdc42 that have crucial role in the organization of actin cytoskeleton during cell movement. They performed three main experiments: The first experiment tested if membrane recruitment of a small part of intersectin (ITSN-DH-PH) that regulates Cdc42, was effectively inducing transient increases of local protein activity. They shown images of local enrichment of biosensors responsive to Cdc42 activity in the membrane that disappeared few seconds after turning off the red laser. The second experiment tested if membrane recruitment of a part of Tiam (Tiam DH-PH domain) was sufficient to induce changes in the shape of NIH3T3 cells. They illuminated the whole cell with red light for 20 minutes and inmediatly after counted the percentage of cells that made new lamellipodia (actin cytoskeletal projection on the mobile edge of the cell). The result was that almost 80% of cells made new lamellipodia under red-light treatment, compared with a 10% of control populations. To make things even more interesting, in a third experiment they pointed a red laser dot on the edge of one cell and gradually moved it outward, slowly extending this red-targeted region from the cell body. They show in movies that they effectively guided the direction followed by the new lamellopodium-- the first reported control of cell movement in real time using light-sensitive proteins!

**More paragraph practice Text for Editing Module 4.1**

**First example**

In assessing the quality of an instrument we distinguish three quality domains, i.e. reliability, validity, and responsiveness. Each domain contains one or more measurement properties. The domain reliability contains three measurement properties: internal consistency, reliability, and measurement error. The domain validity also contains three measurement properties: content validity, construct validity, and criterion validity. The domain responsiveness contains only one measurement property, which is also called responsiveness. The term and definition of the domain and measurement property responsiveness are actually the same, but they are distinguished in the taxonomy for reasons of clarity. Some measurement properties contain one or more aspects, that were defined separately: Content validity includes face validity, and construct validity include structural validity, hypotheses testing, and cross-cultural validity.

**Second example**

The church’s record-keeping system and its high level of accuracy has been previously reported (2). Briefly, the church creates and maintains a church record for each individual who is baptized into the church. These records are created at the congregation level at the time of baptism and then forwarded to the general church level where the membership record is added to the church membership database. These records contain minimal information including name, date of birth, parents’ names, dates of church ordinances, and current address. Each congregation has a lay membership clerk who is responsible for updating the membership records for the members of the congregation. Such updates would include dates of ordinances received after baptism (e.g., priesthood ordination or marriage), name of spouse when a member marries, change of current address and date of death.

While the accuracy of the church record is dependent upon lay clerks within each congregation, each member has an opportunity to review their membership record once a year to check it for accuracy. For this reason and because the church emphasizes accurate record keeping, the information available from the church records is quite reliable, especially for members who are actively involved in the church. When a member dies and the clerk reports his/her death to the Church Membership Council, the membership record is updated and then archived in the church’s deceased membership file.

**Third example**

Previous studies have consistently reported increased risk of subsequent drug use associated with conduct problems and antisocial behavior in childhood (1-5), and an association of drug dependence with conduct problems was found in a general survey of young adults (9). Furthermore, long-term relationships between aggressive, unconventional, and impulsive behaviors have also been found with drug use involvement generally (10-12). However, different pathways between early childhood misbehavior and drug involvement may exist. Psychiatric symptoms and cognitive disabilities may be manifest as aggressive behaviors and drug use may be a response to impulsive tendencies that often co-occur with aggression or misbehavior. Distress and failure to adopt responsible conventional roles and behaviors may be important mediators linking childhood misbehavior to late drug dependence (13,14).

**Text for editing, demo edit 4, Module 4.8 (optional)**

In a recent work on ‘Interactions with Big Data Analytics’, authors Danyel Fisher et.al. talk about interesting developments in the world of analyzing data. Authors define analytics as a term that refers to any data driven decision. An example of application of analytics is Zynga, an online games company that studies how its audience plays the game and uses that data effectively to modify the games.

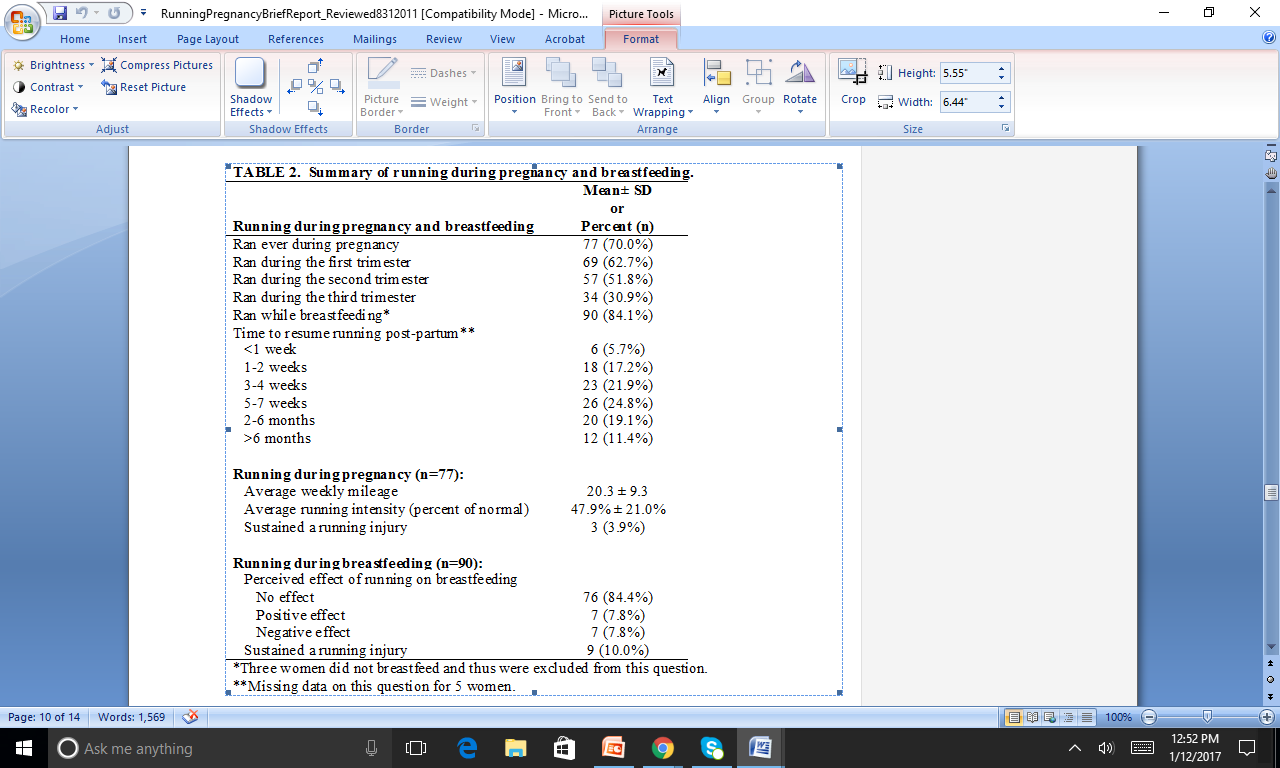
The paper reports the state of practice by interviewing sixteen pioneering analysts in this field. The paper discusses about the definition of big data, contemporary ways of analyzing data, challenges peculiar to big data, and proposes a five step workflow type of an approach to analyzing big data. In our digital lives (interactions through information technology devices) we generate huge amounts of data: social relationships, purchasing behavior, watching of videos, etc. Big Data Analytics aims to construct the big picture from the minutia of our digital lives.

The authors draw a refreshing parallel to the old age mainframe computing where the work would be submitted to massive systems and the results would be obtained after a period of time. Big data analytics, argue the authors, is very similar: that it involves hypothesis and needs huge computing power, that it is often submitted and results are available after a period of time, and that the end user computers are only used for viewing the results and not for processing.

Pivotal contribution of the paper is the generalization of how big data analytics can be approached. Acquiring data, choosing the right architecture for analyzing the acquired data, fitting the data for the chosen architecture, coding and debugging, and fine tuning are the five steps suggested by the authors. This five step process repeats itself as many times as necessary until meaningful results are obtained. The paper cautions the skill gap in bringing the right proportion of scientific flavor in models created by business users.

Of immediate significance, is the potential to apply big data analytics to design more user friendly interfaces, enrich customer experience by analyzing the ways customer uses the product, understand healthcare spending, etc. The limitation is only our human ability to think creatively and harness the exploding world of data.

**Practice writing results Text for Editing Module 5.3**



The majority of runners ran during pregnancy (70.0%, 77/110), with 62.7% running during the first trimester, 51.8% during the second trimester, and fewer than one third (30.9%) during the third trimester (Table 2). From the 77 women who ran during pregnancy, we observed the average weekly mileage during pregnancy for those who ran to be 20.3 ± 9.3 miles. Average running intensity was reported to be 47.9% ± 21.0% as a percent of non-pregnant running effort. A small number (3.9%, 3/77) reported sustaining a running injury while pregnant. About a quarter (24.8%) waited 5-7 weeks to resume running post-partum. A small fraction (5.7%) resumed running less than a week after giving birth. Some women (11.4%) waited more than six months post-partum to resume running.

**Introduction practice Text for Exercise Module 5.6**

**Introduction Practice Exercise 1**  
Identify sentences that give:  
1. The “what’s known” or background  
2. The “what’s unknown” or gaps and limitations   
3. The aims and approach of this specific study

* Mass media in the form of television, radio and printed material are frequently used to deliver medical information to the public. Research suggests that mass media can improve public knowledge[**1**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) and potentially improve health behaviors.[**2**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) Television is one of the most important mass media sources of health information.[**3**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**4**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) However, concerns have been raised about the quality, completeness and accuracy of medical information covered in the news media,[**5**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**6**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**7**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**8**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) and television news media is no exception.[**7**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**8**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) The quality of information outside of the news media has not been examined.
* According to Nielsen’s report, American citizens spend an average of over five hours a day watching television.[**9**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long)International health information programs, such as *The Dr Oz Show* and *The Doctors* have become a regular part of television broadcasting. In the 2012-13 season, *The Dr Oz Show* was consistently ranked in the top five talk shows in America with an average of 2.9 million viewers per day, while *The Doctors* had a high of 2.3 million viewers.[**10**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**11**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) In the 2012 Greatist report, Dr Mehmet Oz and Dr Travis Stork (one of the hosts of *The Doctors*) were both included in the top 100 health and fitness influencers.[**12**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long)
* Popular television talk shows such as *The Dr Oz Show* often engender skepticism and criticism from medical professionals.[**13**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**14**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) [**15**](http://www.bmj.com.laneproxy.stanford.edu/content/349/bmj.g7346.long) However, no research has systematically examined the content of the medical information provided on these talk shows. Our objective was to review the most popular medical talk shows on television, to (1) determine the type of recommendations and claims given and the details provided, and (2) search for and evaluate the evidence behind these recommendations.

**Introduction Practice Exercise 2**

* Scholarly publications are among the most important indicators of academic achievement. While the quantity of papers authored certainly matters, simple publication count is not the only important metric. The reputation of the journal in which a paper is published (often gauged using impact factors), along with the number of citations that a paper receives (i.e., other articles that reference that particular work), are together often seen as proxies for a publication's importance and influence.
* Self-citation may have a consequential impact on scholarly careers by both directly and indirectly increasing an author’s citation counts. Each additional self-citation yields an additional three citations (though not necessarily to the same paper) from other scholars over a five-year period (Fowler and Aksnes 2007). Given the importance of metrics of scholarly influence in academic hiring, tenure and salary decisions, examining gender differences in citation patterns may shed light on persisting gender discrepancies in faculty hiring and promotion. More broadly, academic publishing provides an illustrative case for gender differences in evaluation metrics and workplace advancement.
* Papers authored by women receive fewer citations than do papers by men, even controlling for tenure status, institution, and journal (Larivière et al. 2013). Fewer citations to female-authored papers could be due in part to gender differences in self-citations (when an author cites his or her own previously published work). Research analyzing 12 journals in the field of international relations from 1986-2000 showed men cite their own papers more than one and a half times as often as women (Maliniak, Powers, and Walter 2013).
* To date, studies of self-citation have been few in number and confined to a limited number of disciplines and a relatively small number of papers. Here we examine gender differences in self-citations across 24 broad academic fields with hundreds of subfields and several million scholarly papers, with over a million self-citations. We further examine how the gender ratio self-citation patterns changed over time.

**Text for editing, demo edit 5, Module 5.10 (optional)**

Reactive oxygen species (ROS) are highly reactive chemicals often associated with escalating warfare between pathogens and their hosts. For example, ROS are integral to biological defenses, such as the respiratory burst in phagocytes of animals and programmed cell death in plants, to ward off microbial infections. In a landmark study, published in the journal Plant Cell, Tanaka and colleagues recently uncovered an additional role for ROS as “regulators of symbiosis.”

The team studied a symbiosis between perennial rygrass (Lolium perenne) and a fungus (Epichloë festucae) that lives endophytically (i.e., inside) the grass. The mycelium of this fungus—composed of cells called “hyphae”—colonizes all leaves of the plant, but the hyphae sprout only sparsely in tissues, never breach cell walls or membranes, and grow in perfect synchrony with the leaves of its plant host. This exquisite harmonization of fungal and plant growth directs resources to the production of fungal toxins that protect the symbiosis from herbivores. But how this harmonization is achieved and what its underlying mechanisms are have remained a mystery.

To address this question, Tanaka and coworkers generated random mutations in the E. festucae genome. They used a method called insertional mutagenesis, in which DNA pieces are randomly inserted into the fungal genome in the hope of disrupting a gene resulting in observable growth changes in symbioses with these fungal mutants. They indeed found a mutant showing a highly unusual growth pattern: unlike the synchronous growth of the wild-type fungus, the mutant hyphae showed profuse and abundant proliferation throughout the grass. Moreover, plants infected by this mutant showed poor growth and often died.

This set the stage for the next step: finding the genetic change that had caused these aberrations. Using molecular genetics tools, the researchers homed in on the gene the DNA insertion had disrupted. Surprisingly, only a single integration event had caused this abnormal growth mutant—it had disrupted a fungal gene the researchers named noxA.

To get an idea of what the encoded protein (NoxA) does, the team first compared its sequence with those of enzymes with known activities. They noticed that NoxA was very similar to NADPH oxidases, enzymes that are often involved in generating ROS in cells. Indeed, when the researchers next looked at ROS production in the plant, they observed that ROS accumulated only in plants infected by the wild-type fungus and not in those infected by the noxA-disrupted mutant fungus. This confirmed that NoxA is involved in ROS production required for proper functioning of the symbiosis.

The study by Tanaka and colleagues raises tantalizing questions. Chief among them is what the mechanism is through which ROS help maintain a functional symbiosis. The researchers suggest that ROS could be involved in establishing physical connections between the cell walls of the plant and fungus. Alternatively, ROS may play a role in symbiotic signaling: their short half-life predisposes them for cellular communication, perhaps facilitating an interspecies “Morse code” that helps maintain the symbiosis. If so, identifying the plant sensor and signaling pathways involved could provide deeper insights into how plants recognize and interact with beneficial symbionts and can distinguish them from pathogens.

**Text for editing, demo edit 6, Module 6.10 (optional)**

Sixty percent of world population is afraid somehow to go to the dentist, but fifteen to twenty percent suffer odontophobia. The World Health Organization recognizes odontophobia as a severe fear of the dentistry and of receiving dental care. This fear often leads people to avoid going to the dentist until emergencies happen, requiring invasive treatment which can reinforce their fear of dentistry – the avoidance cycle- . Odontophobia symptoms are hyperventilation, tachycardia, hypertension, sudden drop in blood pressure, transpiration, insomnia, mouth dryness, nausea and vomits among others.

Odontophobia can be treated in combination of behavioral and pharmacological approaches. The use of pleasant odors (like fresh bread or coffee), warm colors of the place, pleasant music, or beautiful paintings on the walls are effective techniques that dentists around the world are using. A recent study from the National Italian Union of Dental Industry showed that sensorial stimuli are decisive from the psychological perspective of patients and can be preferable than the use of anxiolytics. Intraligamentary anesthetics, computer-controlled injections and nitrous oxide sedatives are pharmacological ways that offer no-pain solutions.

The study concluded that dentists can manage odontophobia by taking some simple steps: Transmit serenity and friendliness by taking time to chat with the patient; tell and show what is going to be done (which is especially effective with kids);  offer earphones to isolate them from external sound and at the same time to provide music therapy; adjust the chair to the patient dimensions; provide an image of quality and professional demeanor; offer a well-illuminated place with plenty of space, and offer no-pain anesthetics.

By now, oral hygiene continues to be the best way to avoid going to the dentist, but that doesn’t solve the phobia. Researchers are now focusing on the use of internet as a way to confront anxiety, suggesting the effectiveness of online support communities on helping odontophobics to successfully receive dental care.

**Text for editing, demo edit 7, Module 7.8 (optional)**

Ovarian cancer is the deadliest gynecologic cancer with a high mortality rate that has remained unchanged in the past four decades. The dismal prognosis of ovarian cancer is in large part due to the acquired resistance to chemotherapy. Epithelial ovarian cancer, the most common type of ovarian cancer, is initially responsive to cisplatin therapy. The recurrent disease, however, is often refractory to treatment and leads to mortality. New strategies to overcome drug resistance are urgently needed in order to reduce the mortality rate of ovarian cancer.

The discovery of small interfering RNA (siRNA) by Fire and Mello in 1998 has provided new avenues of combating resistant cancers. Silencing genes that are involved in drug resistance using RNA interference (RNAi) can allow for reversing cisplatin resistance in ovarian cancer. Successful treatment of ovarian cancer cells with multidrug resistance (MDR) gene-silencing siRNAs and cisplatin requires the development of novel vehicles that can specifically and effectively deliver cisplatin to cell nuclei and siRNAs to cell cytoplasms, respectively. We report here the first use of nanoscale metal-organic frameworks (NMOFs) for the co-delivery of cisplatin and pooled siRNAs to overcome drug re-sistance in ovarian cancer cells.

MOFs are an emerging class of self-assembled, porous materials whose properties can be readily tuned by varying the molecular building blocks. When scaled down to the nano-regime, NMOFs serve as efficient nanocarriers for the delivery of imaging contrast agents and chemotherapeutics. We surmised that NMOFs represent a unique nanocarrier platform by virtue of their high porosity and controllable surface functionalities: the large pores of NMOFs can be used to load chemotherapeutics while the metal ions on the NMOF surfaces can be used to bind siRNAs. The simultaneous and efficient delivery of cisplatin and pooled siRNAs to ovarian cancer cells can allow for enhanced anticancer efficacy by blocking multiple drug resistance pathways. In this work, cisplatin and siRNA were sequentially loaded into UiO NMOFs by covalent attachment to bridging ligands inside the NMOFs and coordinating to metal sites on the NMOF surfaces, respectively. UiO NMOFs protect siRNAs from nuclease degradation, enhance siRNA cellular uptake, and promote siRNA escape from endosomes to silence MDR genes in cisplatin-resistant ovarian cancer cells. As a result, co-delivery of cisplatin and siRNAs with NMOFs led to an order of magnitude enhancement in chemotherapeutic efficacy in vitro, as indicated by cell viability assay, DNA laddering, and Annexin V staining.

**Text for editing, demo edit 8, Module 8.10 (optional)**

Ovarian cancer is the deadliest gynecologic cancer with a high mortality rate that has remained unchanged in the past four decades. The dismal prognosis of ovarian cancer is in large part due to the acquired resistance to chemotherapy. Epithelial ovarian cancer, the most common type of ovarian cancer, is initially responsive to cisplatin therapy. The recurrent disease, however, is often refractory to treatment and leads to mortality. New strategies to overcome drug resistance are urgently needed in order to reduce the mortality rate of ovarian cancer.

The discovery of small interfering RNA (siRNA) by Fire and Mello in 1998 has provided new avenues of combating resistant cancers. Silencing genes that are involved in drug resistance using RNA interference (RNAi) can allow for reversing cisplatin resistance in ovarian cancer. Successful treatment of ovarian cancer cells with multidrug resistance (MDR) gene-silencing siRNAs and cisplatin requires the development of novel vehicles that can specifically and effectively deliver cisplatin to cell nuclei and siRNAs to cell cytoplasms, respectively. We report here the first use of nanoscale metal-organic frameworks (NMOFs) for the co-delivery of cisplatin and pooled siRNAs to overcome drug re-sistance in ovarian cancer cells.

MOFs are an emerging class of self-assembled, porous materials whose properties can be readily tuned by varying the molecular building blocks. When scaled down to the nano-regime, NMOFs serve as efficient nanocarriers for the delivery of imaging contrast agents and chemotherapeutics. We surmised that NMOFs represent a unique nanocarrier platform by virtue of their high porosity and controllable surface functionalities: the large pores of NMOFs can be used to load chemotherapeutics while the metal ions on the NMOF surfaces can be used to bind siRNAs. The simultaneous and efficient delivery of cisplatin and pooled siRNAs to ovarian cancer cells can allow for enhanced anticancer efficacy by blocking multiple drug resistance pathways. In this work, cisplatin and siRNA were sequentially loaded into UiO NMOFs by covalent attachment to bridging ligands inside the NMOFs and coordinating to metal sites on the NMOF surfaces, respectively. UiO NMOFs protect siRNAs from nuclease degradation, enhance siRNA cellular uptake, and promote siRNA escape from endosomes to silence MDR genes in cisplatin-resistant ovarian cancer cells. As a result, co-delivery of cisplatin and siRNAs with NMOFs led to an order of magnitude enhancement in chemotherapeutic efficacy in vitro, as indicated by cell viability assay, DNA laddering, and Annexin V staining.