

# Remembering resistance: non-genetic memory in bacteria

Dr Hanna Salman and Dr Andrew Mugler

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# Remembering resistance: non-genetic memory in bacteria

Typically, the skills and properties developed through adaptation during a lifetime may not be directly passed onto the next generation as encoded in genes – they are learnt. However, **Dr Hanna Salman** and **Dr Andrew Mugler**, from the **University of Pittsburgh** in the US, are finding evidence that bacteria can pass on ‘memories’ to their offspring, over several generations. Understanding more about this process is crucial for the fight against the rise of antibiotic resistance in bacteria.



**Dr Hanna Salman**



**Dr Andrew Mugler**

Department of Physics and Astronomy,  
University of Pittsburgh, USA

## Field of research

Biological physics

## Research project

Using experimental and theoretical methods to investigate non-genetic memory of antibiotic resistance in bacteria

## Funders

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**A**ntibiotic resistance is a growing problem that seriously threatens humanity’s collective ability to fight bacterial disease. Scientists from many different fields are working on addressing this issue. One such field is the relatively new discipline of biological physics, which involves taking lessons from physics and applying them to biological questions. Dr Hanna Salman and Dr Andrew Mugler both work in the same department at the University of Pittsburgh but take different – yet complementary – approaches to understanding antibiotic

Talk like a ...

## biological physicist

**Antibiotic** — a substance that inhibits the growth of, or destroys, bacteria

**Bacteria** — a large group of single-celled organisms, some of which can cause disease

**Daughter cells** — genetically identical cells formed when a cell undergoes mitosis

**Mitosis** — a type of cell division resulting in two daughter cells with the

same number of chromosomes as the parent cell

**Messenger RNA (mRNA)** — a genetic ‘messenger’ molecule involved in protein synthesis

**Non-genetic memory** — in bacteria, information or characteristics that are passed on by mechanisms other than through genetic inheritance

resistance. While Hanna’s lab undertakes experiments with bacteria, Andrew’s lab develops mathematical equations and computer programmes that model the outcomes of such experiments. Combined, they are studying a previously inaccessible pathway by which bacteria can potentially develop antibiotic resistance.

## Non-genetic memory

A cell’s DNA is where instructions of how to make all cellular components are stored. It was, therefore, believed that all cellular properties are determined by the DNA, and that DNA was the only carrier of memory between consecutive generations. However, cellular components are produced by complex interactions between cellular machinery and the DNA. This suggests that cellular machinery passed between consecutive generations can

also influence the cell’s memory. Bacteria divide to form two new, identical ‘daughter’ cells via a process called mitosis. This means that, as well as the genetic material, both daughter cells retain other cellular content from the parent cell. “When a cell divides, all of its content is divided between the two daughter cells,” says Hanna. “If a cell happens to have a certain property – more molecules of a specific type, for instance – then this property may be retained in its daughters.”

This process is different from genetic inheritance, because while information encoded in genes is very stable, the cell’s molecular content exhibits large fluctuations, which can lead to deviations in the cell’s attributes from their steady state. “Cellular properties may persist for several cell divisions before the natural



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processes that keep these attributes steady kick in,” says Andrew. “As a result, cellular ‘memory’ can last for multiple generations – longer than the lifetime of the cell itself.”

It is only in recent years that scientists have paid significant attention to this process of non-genetic memory in bacteria. “Previously, it was thought that when cells divide, the ‘memory’ of the previous generation is essentially wiped,” says Hanna. “Now, it has been established that cell properties are subject to complex control mechanisms, but it is still generally assumed that non-genetic memory only lasts a generation or so.” However, Hanna and Andrew’s labs are uncovering evidence that suggests that this memory can persist for multiple generations – which has huge significance for the real world.

### Antibiotic resistance

“Bacterial resistance to antibiotics is a major health concern,” says Andrew. “Often, bacteria are able to develop antibiotic resistance without mutating their genome, by changing their cellular properties.” If this resistance can be passed on through multiple generations, it has the potential to be a big problem. Previously, it was assumed that antibiotic resistance was always inherited genetically, through mutations in the bacteria genome, but non-genetic memory presents a possible second pathway for such resistance to emerge. “We need to understand non-genetic cellular memory in a quantitative way, how it is affected by antibiotics, and the underlying molecular mechanisms behind it,” says Hanna. “With this knowledge, we can potentially reduce or even prevent bacteria’s ability to develop resistance.”

Hanna and Andrew’s teams are investigating how different antibiotics appear to affect this intergenerational memory. “This study will allow us to better understand how cells develop antibiotic resistance,” says Hanna. “In addition, we’re planning to study how the abundance of messenger RNA (mRNA) can affect the cell’s memory.” mRNA is the ‘messenger’ molecule that carries the genetic information stored on DNA to the cellular machinery that uses this information to build specific proteins. “mRNA is also passed on from

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***This study will allow us to better understand how cells develop antibiotic resistance.***

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mother to daughter, so its abundance is likely an important factor affecting cellular memory,” says Andrew.

### Experiment and theory

The teams have been making some interesting findings: specifically, that non-genetic cellular memory can endure for multiple generations. “These findings are at odds with current understanding of how cells control their properties and division cycles,” explains Hanna. “This indicates a gap in our collective scientific knowledge.” The teams are aiming to fill this gap with a two-pronged approach: Hanna’s lab focusing on further experiments, and Andrew’s lab focusing on mathematical modelling. “We aim to develop a fundamental experimental and theoretical understanding of the observed multi-generational memory,” says Andrew.

Both experiment and theory are necessary to build a strong scientific case for these findings. “Experimental results suggest a model of a possible underlying mechanism, but mathematical theory is required to make this model plausible, precise and predictive,” says Hanna. “Conversely, the predictions made by theoretical models need to be tested with real-life experiments.” This collaboration between experimentalists and theorists has been underway in the realm

of physics for decades but is a relatively new approach for biological systems.

Non-genetic memory in bacteria is not simply a matter of generations having more or less of certain molecules. There are complex interactions to account for, which is why sophisticated modelling approaches are needed. “Statistical physics provides the framework for describing fluctuations in cellular properties,” explains Andrew. “These tools allow us to describe how molecular abundances fluctuate in time, and how they depend on one another, ultimately helping us predict the outcome of experiments.” These experiments need to be tightly controlled to be compatible with the model. “We continuously strive to develop new experimental systems to accurately control the environment and perform molecular manipulations,” says Hanna.

### Looking ahead

By understanding the molecular control behind non-genetic memory, researchers can then unlock mechanisms to influence or disrupt this control. “If we understand how this memory is affected by antibiotics, we can influence it to prevent cell adaptation to new antibiotics,” says Andrew. “Additionally, control mechanisms in biology are often common across many different types of cells, so what we learn here may also be relevant to other contexts.” For instance, the uncontrolled proliferation of cancer cells appears to involve a non-genetic change similar to bacterial adaptation, so it is possible that the teams’ findings may be useful for slowing or stopping the spread of cancer.

Hanna and Andrew are aiming to develop ever-more sophisticated approaches to study this multigenerational memory in more detail. “Experimentally, we are working on building new devices and new genetic tools to measure the properties of multiple molecule types in many pairs of daughter cells at the same time,” says Hanna. “Theoretically, we are developing a mechanistic theory of cell division to describe how molecular fluctuations and memory work from the molecular to the cellular scale,” adds Andrew.

# About *biological physics*

**B**iological physics is an interdisciplinary field that takes approaches most typically used by physics to study biological questions. As it becomes easier to develop large and complex datasets of biological information, there is increasing value in using quantitative methods to analyse this data. This can involve any area of biology, from bacteria to ecology, biotech to genetics.

Biological physics is a relatively new field, which means it still has a way to go to truly reach its potential. “Despite the significant efforts devoted to biological physics over the last two decades, there are still so many questions that we haven’t touched on yet,” says Hanna. “The experimental and theoretical tools that are currently being developed in the field will make a wide range of questions addressable for the next generation of biological physicists.” Hanna believes that these questions will address some of the fundamentals of life: the fine details of how organisms learn, reproduce and evolve.

Powerful new tools for data collection and analysis are making biological physics methods increasingly possible. “The interface of physics and biology is a rapidly growing field,” says Andrew. “Experiments are increasingly quantitative, and data analysis is increasingly benefitting from advanced computational tools.” This opens new doors for data-driven biology, providing the tools for applying physical modelling techniques to biological questions.

## Pathway from school to *biological physics*

- At high school and college, subjects such as physics, mathematics, computer science and biology will provide a good groundwork for working in biological physics.
- Hanna and Andrew say that a university background in physics, rather than biology, provides a smoother path into biological physics. Andrew adds that an increasing number of undergraduate courses are incorporating both early on. Hanna emphasises that becoming an independent learner is crucial, particularly for a newer field like biological physics, which needs innovative ideas to advance.

## Explore careers in *biological physics*

- Andrew recommends exploring the Division of Biological Physics ([engage.aps.org/dbio/home](https://engage.aps.org/dbio/home)) within the American Physical Society, especially its new journal, PRX Life ([journals.aps.org/prxlife](https://journals.aps.org/prxlife)), to gain an understanding of the field.
- Hanna points to three Physics Frontiers Centers focused on biological physics, all of which offer outreach and education programmes. They are The University of Chicago’s Center for Living Systems ([centerforlivingsystems.uchicago.edu](https://centerforlivingsystems.uchicago.edu)), Princeton University’s Center for the Physics of Biological Function ([biophysics.princeton.edu](https://biophysics.princeton.edu)) and Rice University’s Center for Theoretical Biological Physics ([ctbp.rice.edu](https://ctbp.rice.edu)).
- Hanna’s lab collaborates with Pittsburgh public schools to offer internships to high school students. Get in touch with the Salman lab: [salmanhanna.wixsite.com/salman-lab](https://salmanhanna.wixsite.com/salman-lab)
- According to Salary.com, the average biophysicist salary in the US is \$72,600.



## Meet Hanna

**I have always wanted to understand why and how natural phenomena occur.** I find it exciting whenever I finally understand why things around us behave the way they do. This passion was in part inspired by my dad, who was a high school physics teacher. He saw my aptitude for science and encouraged me to pursue it.

**The road to an independent academic position in science is very long and often difficult.** To go through it requires hard work and a lot of support and encouragement along the way. Every experiment that succeeded after much work, and every word of support and encouragement I received from my advisers, were the eureka moments that gave me confidence that I could make it as a scientist.

**In addition to making new discoveries in research and understanding how the world around us works,** the most rewarding thing of leading my own lab is to see my students grow as scientists, become independent and accomplished researchers, and achieve their own career goals.

**When carrying out new and innovative research, many attempts will fail.** This might discourage new students from continuing the work and trying new ways to achieve their goals. The most challenging thing as a group leader is to maintain students' motivation in the face of these failures.

**There are several scientific discoveries that I am proud of,** but what I am most proud of so far is that all my students were able to reach the next milestone they wanted to achieve upon completing their work with me, and which advances them toward the career goals they set for themselves.

**What initially attracted me to biology is that unlike inanimate systems,** biological systems can vary in their behaviour under the same environmental conditions. I am currently working toward understanding how this variability develops over time and how information passed on from one generation to the next allows for this diversification. We have recently developed a new experimental tool that can help us shed some light on this question, and I hope that we can use it to answer this question, in the near future.

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### Hanna's top tips

1. Make sure that you really love your chosen research area and have genuine interest in it.
2. Don't just follow trends; they will fade and change with time, and only by being interested in what you do will you overcome challenges and keep the motivation to achieve your goals.



## Meet Andrew

**I always loved mathematics and art.** I found that science, especially physics, combines aspects of both, because it requires creative problem solving. I also had a dedicated and dynamic high school physics teacher who pushed me to pursue science.

**I considered leaving graduate school to teach,** but I realised that research-focused careers often include the freedom to teach, whereas teaching-focused careers rarely allow for extensive research. I'm glad I chose this path because I love doing both.

**It is deeply rewarding to see a graduate student go from knowing nothing about a field** to becoming an expert and, essentially, begin teaching me! I also love solving puzzles, so it is personally rewarding to have that be a part of my livelihood and get to share that with others.

**It is challenging to sustain a steady stream of new ideas.** It requires staying very engaged with the field and foreseeing where my group can contribute meaningfully.

**Although I have won several early career awards,** I am proudest of an award I won with others: the American Physical Society's Oppenheim Award. It honours the best paper in Physical Review E, a specialised biological physics journal. It is not the most prestigious award, but I am proud because my student was the paper's first author, and it means that people really engaged with and enjoyed the paper.

**I am also proud that undergraduate students I have advised on research projects** have won some of the highest awards available, including a Fulbright Scholarship and the American Physical Society's highest undergraduate award.

**The past few decades have seen a huge advance in our understanding of the molecular interactions** that drive cell behaviour, but new technologies are generating more data than ever before at the cellular and population levels. A primary goal of mine is to take the mathematical tools from physics that I have applied to molecular interactions in the past and apply them to cell- and population-level interactions in the future.

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### Andrew's top tip

Aim to gravitate towards the subjects and people who interest you most. You don't have to know what you will be doing in five or ten years from now, but if you explore and trust your instincts, you will find yourself doing what you love and are good at.



# Biological physics

with Dr Hanna Salman  
and Dr Andrew Mugler

## Talking points

### Knowledge

1. What is non-genetic memory?
2. What is antibiotic resistance?

### Comprehension

3. Why do Hanna and Andrew combine experimental and theoretical approaches within their work?
4. What has their collaborative team discovered that appears to go against current understanding of non-genetic memory?

### Application

5. What sorts of challenges do you think might arise when an experiment-focused team and a theory-focused team work together? How might Hanna and Andrew overcome these challenges?
6. How do you think the team's findings might help fight cancer? What biological processes might be disrupted to do so?

### Analysis

7. Hanna says that theoretical models are needed to make experimental models "plausible, precise and predictive". What do you think he means by each of these adjectives, and why is each important to science?
8. Why do you think the team's discoveries about multi-generational non-genetic memory were not made earlier? Why might they have been missed by other scientists?

### Evaluation

9. Antibiotic resistance is a growing problem; bacteria appear to be gaining resistance to antibiotics faster than we are discovering new antibiotics. What measures do you think that individuals, healthcare systems, scientists and the food industry should take to prevent this becoming a crisis? Do some online research if you are unsure of how to answer.
10. Why do you think that the growth of biological physics has accelerated in the last couple of decades? What do you think might have limited its emergence before then?
11. Where do you see biological physics leading in the future? What do you think future biological physicists will research?

## Activity

Take some time to research the field of biological physics, in particular some of the big societal issues that it is attempting to tackle. Choose one such issue that captures your attention. There are many issues to choose from, including:

- Solutions to antibiotic resistance
- Personalised medicine
- Tracking sources of pollution
- Developing biology-based renewable energy sources
- Genetic screening (e.g., to understand individuals' vulnerabilities to certain diseases)

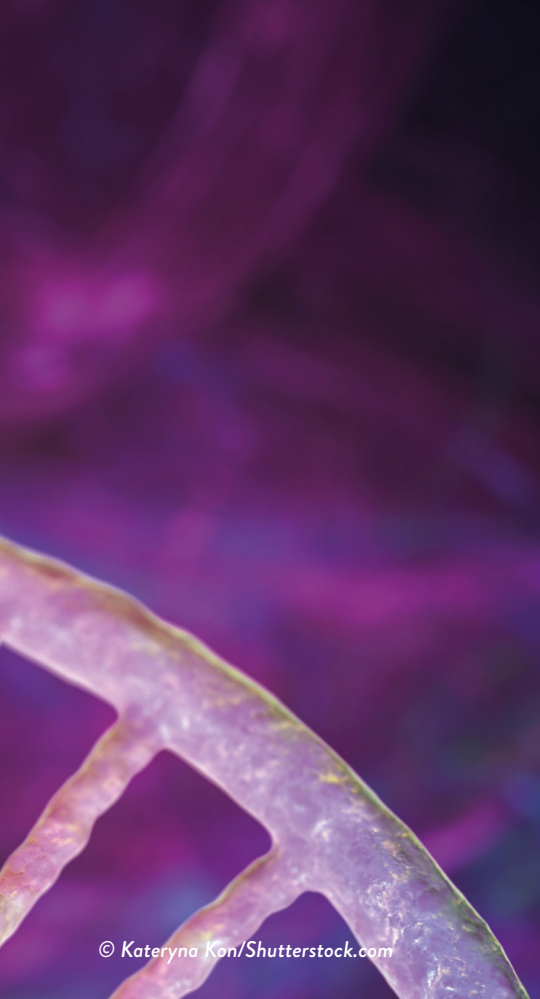
Now, imagine a future where research in this area has reached a milestone and is ready for application in the real world. Design a presentation to promote this research output. Your presentation should include:

- An introduction to the problem
- An overview of relevant research (including both real research to date, and imagined future research)
- Key findings and how they led to this major output
- How the research output works to solve this problem, and what benefits it can be expected to bring
- Next steps for rolling out this output into the world – to include any controls or regulations it might need.

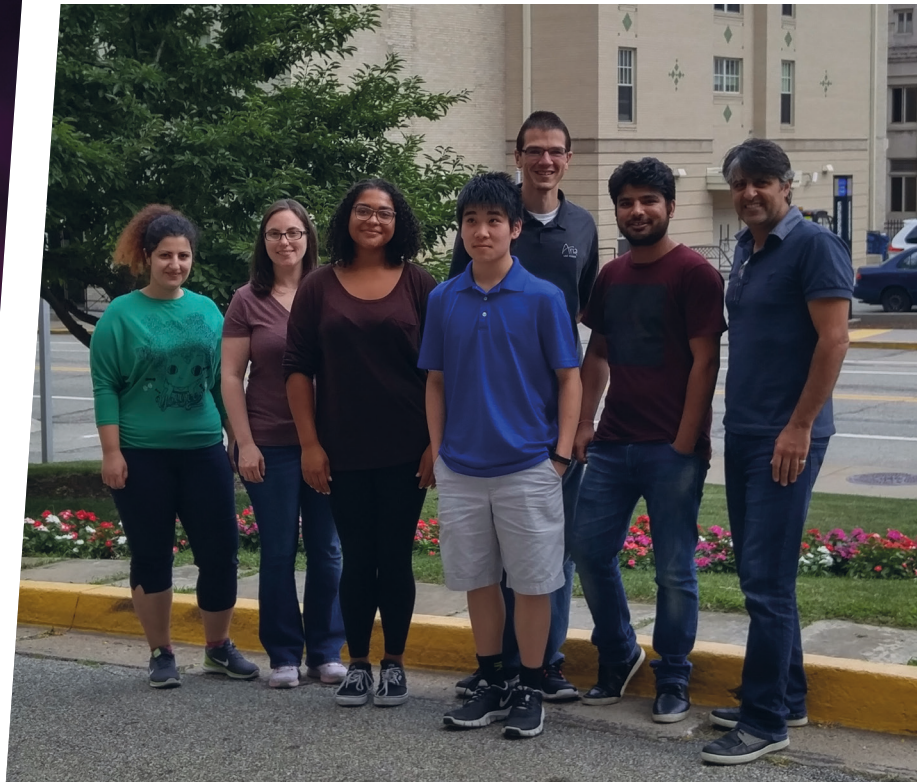
Present to your class and take any questions raised. Was your audience enthused about your imagined output? How likely do you think the future will see this scenario become a reality? What related research areas would you like to learn more about?

## More resources

- The Biophysical Society provides a quick introduction to biological physics and its applications: [www.biophysics.org/what-is-biophysics](http://www.biophysics.org/what-is-biophysics)
- The Physics of Life review examines the accomplishments of biological physics to date and how its unique traits are helping answer some fundamental questions: [nap.nationalacademies.org/catalog/26403/physics-of-life](http://nap.nationalacademies.org/catalog/26403/physics-of-life)
- This video from SciShow explains antibiotic resistance and why it is such a complex issue: [www.youtube.com/watch?v=pkTalaQsRIw](https://www.youtube.com/watch?v=pkTalaQsRIw)



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## Photo montage

**Top row:** Dr Hanna Salman (right) with his graduate students Harsh Vashista (second from right) and Maryam Kohram (left) and a team of high school science teachers and students who participated in an outreach summer programme for lab training

**Middle row:** left: Dr Hanna Salman and Dr Andrew Mugler use experimental and theoretical methods to investigate non-genetic memory of antibiotic resistance in bacteria. © Christoph Burgstedt/Shutterstock.com

**Right:** Dr Andrew Mugler with PhD students Michael Vennettilli and Soutick Saha, and postdoc Dr Ushasi Roy

**Bottom:** PhD student Ryan LeFebre and Dr Andrew Mugler. Photo credit Aimee Obidzinski

+44 117 909 9150  
info@futurumcareers.com  
www.futurumcareers.com

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