Introduction

On January 30, 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) in light of the COVID-19 outbreak. In a short space of time, countries mobilized to attempt to contain the virus through travel restrictions, national lockdowns, and an unprecedented collective effort to develop treatments and vaccines.

All around the world, any sense of normalcy soon vanished. In India, for example, millions of workers were suddenly left unemployed and unable to return home due to the closing of factories and businesses. European countries were forced into national lockdowns, rendering many unemployed. For those that weren't, working from home became the new normal for some, while essential workers continued to keep countries afloat. In South Korea, highly sophisticated track-and-trace programs were initiated at an unprecedented pace to contain outbreaks.[1] Meanwhile, certain political leaders, despite an abundance of evidence to the contrary, continued to pursue a dismissive line, claiming that the effects of the virus were vastly exaggerated – all while millions were being infected and perishing from the effects of the virus. The world had changed in the blink of an eye.

The emergence of a new public health threat also had an immense effect on science. Scrambling to understand the virus, scientists and clinicians reoriented their focus toward its effects on mankind. They put their primary areas of research on hold to pursue COVID-19 research, working on projects spanning from SARS-CoV-2 diagnostics to investigating the effect of the virus on rates of cardiac arrest, to how lockdowns were affecting mental health in adolescents.[2] Clinical trials testing possible treatments were initiated and run at lightning speed, an impressive feat of international collaboration between countries and institutions previously unseen at such a ferocious pace.

However, these changes in the direction and rate of research, while largely necessary, also resulted in several potentially negative consequences. Firstly, the literature surrounding the pandemic exploded in quantity. One estimate suggests that by June 2020, not even six months after the PHEIC was declared by the WHO, a staggering 20,000 unique manuscripts about COVID-19 had already been published, increasing by approximately 2,000 a week at the time.[3] The rate of publishing led to what some dubbed an "infodemic," where the volume of new information was overloading our ability to process and make sense of it. The need for scientific speed unintentionally ended up hurting us. Ironically, in an attempt to understand the consequences of the virus more clearly, we had exposed ourselves to information-induced disorientation.

The quality of research suffered too; a large proportion of the manuscripts posted online were preprints, meaning that they were posted without formal peer review to ensure rapid dissemination, making them more error-prone and often less comprehensive. Anecdotal

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evidence suggests "that preprints [were] being used to share more work-in-progress data than a complete story," which is supported by the fact that COVID-19 preprints, on average, were 2,711 words shorter than non-COVID-19 preprints.[3]

Others were concerned by the drastic change in scientific direction. Efforts pivoted en masse toward COVID-related research – an effect dubbed "Covidization" – seemingly neglecting other pressing health issues such as malaria, cancer, and HIV. Madhukar Pai, in a piece in the journal *Nature Medicine*, highlighted that "we need to acknowledge that all health research cannot be about a pandemic or infectious threats, and all infectious-disease research cannot be about COVID-19."[4] The trajectory of medical discovery had well and truly changed.

Thinking in Trajectories

Science works in trajectories. Whether we look from an individual, institutional, or international perspective, we focus our efforts on certain scientific pursuits and omit others. In an ideal world, of course, our efforts would be omnific in nature, pursuing every conceivable scientific trajectory to understand the world with near-perfect precision. At some point, however, we are forced to make a choice to pursue path A or path B – limited by resources, attention, and time. Frustratingly, knowing which path is likely to be most fruitful is often highly unpredictable. On the bright side, this also makes the discovery of new knowledge exciting.

Scientific trajectories thus describe changes in scientific knowledge, concepts, and theories over time. But to better understand the development of these trajectories, we can break them down into their two essential components: rate and direction.

The rate of new discoveries, simply put, can be defined as the amount of scientific progress (defined later in this chapter) achieved over a given amount of time. Scientific direction, on the other hand, is which questions and ideas we focus on in each moment. In the Covidization example above, the direction of discovery among scientists shifted from their primary areas of interest to COVID-related research. These two concepts also interact. By changing the direction of research, we reduce the rate of medical science progress in one direction and increase it in another – a type of scientific agility. As such, maximizing medical progress is highly dependent on choosing the right research directions to pursue.

These two components comprise the foundation for the essential question of this book: *what are the forces that determine the rate and direction of progress in the medical sciences?*

Investigating the rate and direction of progress is not entirely novel. A seminal book from 1962, titled *The Rate and Direction of Inventive Activity: Economic and Social Factors*, investigated the factors that influenced invention, albeit from an economic perspective. It consisted of a series of papers presented at a conference held in the spring of 1960 in Minnesota.[5] In one chapter, Kenneth Arrow, an American economist, highlights how "there is bound to be some discrimination against investment in inventive and research activities" given the risky nature of these pursuits. He realized that the direction of pursuits would be shaped by incentives and context, whether financial or not.

The work in this time period was the first modern investigation of the factors that can lead to distortions in the rate and direction of progress, particularly from a quantitative perspective. The contents of this book build on a similar spirit, focusing instead on progress in the medical sciences. At this stage, it is important to clarify what I mean by the medical sciences. Medical science is a broad term that encompasses the scientific subfields that

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contribute to our understanding of medicine and how the human body functions. As such, it encompasses fields such as biomedical science, the life sciences, human genomics, drug development, and clinical pharmacology. It covers many of the essential research phases and pursuits that underpin modern medicine and our understanding of the human body. The scientific trajectories that will be discussed will be investigated in the context of this definition.

This book is about why we know what we know, and perhaps more importantly, why we don't know what we don't know. Fundamentally, it is concerned with untapped scientific potential.

Why is this important? Firstly, power. Understanding the forces that determine progress allows us to reflect on whether progress is skewed toward the powerful; taking the example to the extreme, it allows us to reflect on whether any actors are to some extent monopolizing progress and thereby monopolizing the medical future. Given the potential of medical discoveries to improve the lives of individuals, either before or after they become patients, there is a need to understand whether certain people are particularly disadvantaged in gaining access to treatments that might help them in the future.

This leads us on to the next important point: morality. There are moral implications associated with certain forces being overly influential in determining what kind of progress is achieved. In a worst case scenario, progress fails to include components that might improve the lives of the common person, circumventing knowledge that would be to the benefit of society – in favor of vested interests shaped by those calling the shots. The right to health can be undermined if medical progress systematically undermines the future health of some for the benefit of others.

Thirdly, understanding the trajectory of discovery is a matter of efficiency. Given the finite resources that exist (financially, timewise, and with regard to human resources), society should be interested in ensuring that we attain the most "bang for one's buck," or value for money. Understanding the forces that drive the rate and direction of medical progress allows us to readjust the trajectory, ensuring that we are spending these finite resources on the right kind of progress.

Defining Scientific Progress

Progress is, of course, a fickle term. The "right" kind of progress is context-specific, driven by public discussions surrounding what we value as a society. It is therefore also a normative concept. Progress necessitates that going from A to B is an improvement of sorts, not simply a change or development. Put another way, point B must be better than point A, which is why values are important. Values allow us to determine whether a change from A to B constitutes true progress or whether it simply constitutes change.

The term *scientific progress* has also been a topic of much debate, culminating in a wide range of definitions. For the sake of simplicity, scientific progress can historically be divided into two main approaches: a cumulative approach and a problem-based approach.

The cumulative approach itself can be further split into two approaches. The first suggests that scientific progress occurs with the accumulation of scientific *knowledge* over time, whereas the competing approach suggests that it is the accumulation of scientific *truths*, or verisimilitude ("truthlikeness"). While knowledge is the information and understanding that we have about a certain entity, which must also be true, truth is the state or quality of being true.

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This cumulative approach was fashionable particularly during the Enlightenment period (late seventeenth to the early nineteenth century), where a belief in endless progress was a fundamental distinguishing characteristic of the time.[6] Auguste Comte, a nineteenth-century French philosopher, noted that "by accumulating empirically certified truths science also promotes progress in society."[7] It was a simple and elegant model of progress.

If we follow the accumulation model, regardless of whether one believes truth or knowledge to be more important, the goal of science is to create as much distance from a particular starting point as possible. For example, given a starting point of no knowledge or truth, medical progress becomes purely forward-looking, aiming to discover the unknown. Practically, though, this then makes it impossible to define whether progress has been made until we look backward in time, given that we don't know what the overall goal is going forward. We realize progress has been made by reflecting on the scientific distance covered.

During the twentieth century, this way of thinking was challenged by scholars, who insisted on shifting from an accumulation-based model to one that is aims- or problem-based. The proponents of this shift highlighted that progress in science "is not cumulative or continuous: the earlier results of science will be rejected, replaced, and reinterpreted by new theories and conceptual frameworks," making it insufficient to classify progress simply by an accumulation of knowledge or truth.[7] The problem with an accumulation model is that there is in fact no alternative; we are always producing more knowledge, regardless of whether this is intentional or not, making progress irrefutably inevitable according to the accumulation model. Thus, while elegant, it isn't as informative as we might think.

Larry Laudan, a prominent philosopher of science, noted that science was instead a problem-solving activity, which was in concurrence with other contemporaries such as Thomas Kuhn, Karl Popper, and Paul Thagard. This was a problem-centric view of science.[8] They posited that simply gaining more knowledge didn't necessarily constitute scientific progress – instead, science progresses when we solve problems that were previously unsolved. The word *progress* will be used frequently throughout the book, which is why it's imperative to explain what is meant by the word up front. In this book, scientific progress follows the problem-centric view as explained by Larry Laudan, with progress largely being measured by how successful science is at solving problems that help the common person through life and disease – not, for example, by how much we succeed financially through scientific ventures. This line of thinking follows in the footsteps of the relatively recent phenomenon in science policy forums of focusing on *responsible research and innovation* and the need to ensure that science benefits the public.[9]

Some may disagree with this approach, either with regard to the problem-centric view or the types of problems that need to be solved. Any disagreement here is not crucial to understanding the contents of the book. Most of the book is concerned with the *mechanisms* that shape the rate and direction, also known as the *how*, which largely holds true regardless of one's approach. Granted, this may still lead to disagreements regarding the implications of these findings. While I do express thoughts regarding the consequences of the scientific mechanisms at play on society, the implications will need to be adjusted to suit local contexts if they are to be useful in guiding future science policy, particularly due to the normative nature of progress.

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Setting the Stage: The History of Approaches to Science

Already in the late 1800s and early 1900s, Bolesław Prus and Florian Znaniecki, a Polish philosopher and sociologist respectively, were interested in predicting future scientific discoveries.[10] Florian Znaniecki in particular, given his background as a sociologist, was interested in establishing a data-driven approach to the social processes of science, rather than relying solely on qualitative evidence. However, any significant progress on this front was limited by a lack of empirical data to make such a study feasible. Gradually, interest in the question of how science works began to flourish more broadly, particularly during the mid-twentieth century.

Vannevar Bush, head of the Office of Scientific Research and Development (OSRD) in the United States, was commissioned by President Franklin D. Roosevelt to put together a report concerning how the country could implement learnings from World War II to further science.[11] The landmark report, titled *Science – The Endless Frontier*, was eventually published in 1945. For many, it represented the first modern piece of scientific policy. The 30-page report was full of suggestions on how scientific policy might be improved. While not all the recommendations were eventually implemented, it did lead to the establishment of the National Science Foundation (NSF) in 1950, which to this day plays a major role in directing scientific policy. In addition, the report "called for a centralized approach to government-sponsored science, largely shielded from political accountability."

In fact, the report very explicitly highlighted the importance of basic scientific research. Basic science, also known as fundamental or pure science, denotes research that is driven by curiosity to expand our knowledge. It doesn't inherently aim to solve any specific problems, but rather seeks to broaden our knowledge base of fundamental phenomena. The report noted that basic research "creates the fund of new knowledge from which the practical applications of knowledge must be drawn."[12] For example, investigating the functioning of cells or DNA does not necessarily solve any concrete problems; rather, it sets the foundation for problem-oriented research to occur afterwards.

This type of problem-oriented research, also known as applied research, is more focused on solving practical problems such as finding treatments for a certain disease. Applied research is thus enabled by applying knowledge from basic research. The distinction between basic and applied research is a crucial one and will appear numerous times in future sections.

The Vannevar Bush report was thus unique in that it was one of the first instances where the significance of basic research was highlighted. Granted, others had made similar points previously in the United Kingdom and the United States in the 1920s, but the timing of the report was ideal. Following the war, it capitalized on a public sentiment highly receptive to science as a contributor to public welfare.[11]

While the report laid the groundwork for the structural approach to science policy, at least in the United States, there was a more ideological battle unfolding at a similar time of a more philosophical nature. The fundamental question at hand was how scientific revolutions occur and how science proceeds. To avoid overcomplicating the competing ideas, it is fair to focus on two different approaches: the approach substantiated by Karl Popper and the approach supported by Thomas Kuhn.

Karl Popper, an Austrian–British philosopher, was of the belief that science proceeds through a process of falsification. He suggested that the first step in science is making conjectures about the world, and thereafter testing their worth – this is what he refers to as

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the logic of discovery. As he put it, scientists "identify certain problems in the world, propose theories to resolve them, and then seek to falsify these theories."[13] For these theories to be validated, and to hold true over time, we must compare these theories against all other theories; in essence, our theories are constantly being challenged. If a contradiction within the theory is found, then we must reevaluate the theory by probing it further; if it doesn't stand up to scrutiny, we discard the theory and must replace it with a new one – one that better explains the problems we have identified. The process is almost Darwinian in nature; the best theories survive while the weakest (identified through falsification) die out.

This approach to how science proceeds, however, was superseded by another process, one outlined by Thomas Kuhn in his seminal book *The Structure of Scientific Revolutions*. Fundamentally, they disagreed on how theories in science were to be treated.[14] Popper held the belief, as described above, that they were to be constantly scrutinized. Kuhn, on the other hand, found little evidence of attempts at falsification in real life, suggesting that practically speaking, constantly trying to falsify theories is not what scientists do. Rather than incessantly challenging theories, he believed that scientists mostly spend their time developing and defending theories.

Kuhn, a philosopher and physicist, distinguishes between what he calls *normal* and *revolutionary* phases in science. Normal science is characterized by a sense of stability; in terms of time, it constitutes the vast majority of work done in science. In this phase, scientists work within a common intellectual framework, also known as a paradigm. A paradigm is the common understanding, as well as the common set of rules, that scientists agree on collectively to adhere to within a given field.

Normal science is thus concerned with solving the scientific puzzles that exist within the framework established by a paradigm. However, these paradigms do not exist forever. Once scientific anomalies within the given paradigm reach a critical mass, a period of crisis ensues. To resolve the crisis, a new revolutionary phase commences, eventually resulting in a new paradigm – the process being known as a paradigm shift: "Scientific revolutions are inaugurated by a growing sense, again often restricted to a narrow subdivision of the scientific community, that an existing paradigm has ceased to function adequately in the exploration of an aspect of nature to which that paradigm itself had previously led the way."[15]

According to Kuhn, scientists thus exist in an *essential tension*, stuck between a desire for innovation and the necessary conservativeness that working within a paradigm requires.[16] This tension is one of the reasons that revolutions are exceedingly rare. As we'll see in future sections, this essential tension is a common dilemma among scientists, which has implications on both the direction and rate of progress, because while "conservative strategies serve individual careers well [they] are less effective for science as a whole."[17]

Both Popper's and Kuhn's approaches have some inherent flaws, although any model that attempts to describe science perfectly is bound to fail. A common aphorism in statistics is that "all models are wrong, but some are useful," which is surprisingly apt in describing the processes and scientific models discussed above. Kuhn created perhaps a more realistic model of how science actually works, whereas Popper to a greater extent described how science ought to be. Both are useful, none are perfect.

One of Kuhn's great worries was that we would eventually get stuck in a perpetual state of normalcy, whereby science failed to enter any more revolutionary phases. This is a valid concern. When we discuss the trajectories of medical sciences in future sections, much of the discussion will center around what happens in normal periods of science. However, part

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of the discussion will also be concerned with how we might induce more revolutionary phases.

Normal periods of science are important; they allow us to refine science to improve its usefulness in the world. But at a certain point, breakthroughs need to take place to avoid ending up in a scientific rut. Finding this balance is key; constantly revolutionizing scientific fields makes them unstable, particularly if we don't agree on the set of rules that govern paradigms. On the other hand, stagnation is also a threat. Understanding the levers that determine the rate and direction of progress will ultimately be crucial in optimizing this scientific balancing act.

Why Now?

The genesis of this investigation into the rate and direction of medical progress was motivated by a three-stage progression in sentiment: admiration, frustration, and curiosity. Like many that go into the medical profession, and into science more broadly, there is an idealistic fascination inherent in the way that science can contribute to the greater good. Personally, I too had a deep admiration for the researchers that drove progress in the medical sciences. Relatively early on in medical school, I had the chance to work on a research project of my own. I felt privileged to be granted access to this new world and see its inner workings. With a completely fresh set of eyes, research initially seemed to be a pure pursuit of truth.

Over time, however, this sentiment slowly morphed from admiration to frustration, not toward individual researchers, but rather toward the system more broadly. It seemed to me that there was a vast amount of scientific potential that was going to waste, simply because the incentive structures underlying the academic community seemed to reward the wrong things. The same diseases seemed to be hoarding attention while others were banished to the opinion section of scientific journals – written by researchers warning of their neglected status. As a newcomer to the field, my impression was that medical research, despite its already significant contribution to society, had a lot more to give.

Instead of simply languishing in this frustration, it became apparent that investigating the incentive structures within the field might result in some lessons that could lead to changes down the line. Initially, my main curiosity centered around the power structures that dictate medical science. In other words, is anyone monopolizing the future of medical breakthroughs?

However, I realized that such a pursuit would be naive without understanding the mechanisms that drive the rate and direction of progress. The thinking was that by identifying the *how*, which is the essence of this book, it might be possible to evaluate the power structures more comprehensively in the future. Recently, the convergence of several different fields has made such a pursuit more feasible – and has made this book possible.

The evidence provided in this book is of two natures: qualitative and quantitative. The qualitative features have always been available, whether through the accounts of science historians or in detailed scientific reports. This anecdotal aspect is key; it nuances the arguments and makes the examples more salient and memorable. But quantitative evidence provides a further layer of evidential depth, particularly relevant for those who seek a more numerical view of progress. The ability to integrate this quantitative aspect is a much more recent phenomenon, driven by advances in data, analytics, and cooperation. The recent work of researchers within this field has enabled us to explore which factors influence the rate and direction of medical science in a way that was previously unthinkable.

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One of the newest fields within this sphere is known as the "science of science," or SciSci. SciSci is "based on a transdisciplinary approach that uses large data sets to study the mechanisms underlying the doing of science – from the choice of a research problem to career trajectories and progress within a field."[17] In particular, physicists, mathematicians, and network scientists have worked to create complex networks of information that provide a new perspective on how scientific pursuits are linked.

Unlike before, this allows us to take a macroscopic view of scientific progress, the choices that scientists make with regard to research, and how collaboration occurs within and between institutions. These methods are potentially groundbreaking, but they are also often based on bibliometric metrics (such as citations – discussed later) which are imperfect measures of scientific value. As these methods mature, however, the hope is that they may allow us to reevaluate and refine our understanding of how science progresses.

Equally important is the growing interest of economists in the field of science. Research in the medical sciences is big business. For example, in the United States, one estimate suggested that a staggering 192 billion dollars had been spent on medical and health research in 2018 alone.[18] While the United States is a leading force with regard to financing research, it isn't hard to imagine the scale of these investments when taking account of the money spent everywhere else.

Unsurprisingly, the scale of these investments has led to economists being increasingly interested in figuring out how best to allocate research funds. Another term for this is allocative efficiency, which describes to what extent resources and goods are distributed optimally. In this case, the argument goes that research funds should be allocated to areas where the output is greatest. An economist, a doctor, and a biomedical researcher might disagree on how we should measure output in this case, whether it's the number of new patents or new treatments for diseases; but the work of economists has certainly added a financial perspective to the question of which factors influence the rate and direction of progress.

In fact, where SciSci and economics meet is through the nascent field of science innovation, seeking to understand the drivers of scientific innovation and using the insights of both fields. Taken together, the advances in our ability to analyze data about science, the increasing interest of economists, and the detailed accounts of science historians has created the evidence base on which this book relies.

The Structure of the Book

The book is divided into four main sections, representing the different stages of a research trajectory: the initial trajectory (Sections 1 and 2), the forces that can bend the trajectory (Section 3), and a reflection on where the trajectory has left us (Section 4).

Sections 1 and 2 outline the factors and mechanisms that determine the initial direction and rate of research pursuits. In other words, we'll look at why we choose to investigate certain scientific problems and neglect others. Scientists, companies, and policymakers exist in a complex ecosystem that affects the choices that they make. Section 1 is thus concerned with the nonfinancial incentives and contextual factors that determine why certain research paths are pursued and why others may be neglected. We will explore a wide range of factors and mechanisms ranging from the role psychological biases to the role of regulation on the initial trajectory of discovery.

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In Section 2, our focus will shift toward the financial determinants of discovery. Funding mechanisms for science undoubtedly play a key role in the pursuit of new discoveries, but how do they affect the rate and direction? We will explore how the funding system affects the research areas we choose to prioritize, as well as how the vested interests of different funders such as governments, private corporations, and foundations influence medical research. This part is heavily reliant on research regarding the economics of science and innovation.

In Section 3, we will shift our focus away from the initial conditions that influence the trajectory and instead focus on the factors that directly influence how the trajectory bends or changes. While the conditions outlined in Sections 1 and 2 define the initial trajectory, there are also several factors that can directly bend scientific trajectories in new directions and change the rate of discovery. Among other factors, we will consider the role of patient organizations, the entrance of new researchers into a field, and the impact of serendipity.

To reflect on the findings from the previous parts, Section 4 is concerned with the implications of these factors as well identifying themes that persist in each of the previous parts. It will also allow us to contextualize the findings to guide actions going forward to ensure that we make the right kind of progress.

To be clear, the book isn't an attempt at soothsaying. It is incredibly difficult to predict the individual choices that a scientist will make in the future – which can be influenced by anything from family matters to sheer chance – but the aggregate choices of many scientists do follow certain trends; it is these macro-level trends that we are interested in. Nor is the book intended to be encyclopedic. A book documenting every possible factor that affects the trajectory in every possible context would be many thousands of pages long, and quite frankly a bore to read. I have attempted to distill these possibilities down to the minimum amount of information necessary to understand how medical scientific trajectories are affected, and in turn, how these affect progress.

In addition, it is also necessary to point out the limits of this book. The topics discussed refer to the discovery of new medical knowledge but are not concerned with their implementation. For example, while we will discuss drug development, for the sake of brevity, we will not be concerned with how they are priced and sold on the market, as important as this may be for patients. Such a compromise is necessary to maintain a focus on the discovery aspect of medical knowledge. Additionally, evidence in the space is rapidly increasing; the book presents the knowledge we currently have about the factors that influence the rate and direction of progress. With time, however, our understanding must undoubtedly be refined. This book thus serves as a preliminary departure point for future discussions regarding the trajectory of discovery.

Lastly, to explain the mechanisms that determine the rate and direction of progress, examples of these mechanisms will be discussed and dissected. These examples may seem to display medical research in a bad light by exposing the flaws that exist in the current system. The intention is not to undermine our trust in medical science, but rather to elucidate the scientific potential that we are failing to maximize. It is exactly because medicine is so pure in its purpose that we have high expectations of it. My hope is that this book will demonstrate how medical science progresses, as well as how we might improve the practice of medical research for the greater good.

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