

Pioneering Adaptive Drug Discovery through Evolutionary Medicine

Shanza Khanum¹, Muhammad Asad^{1,*}, Ahmed Muneeb², Hafsa Iqbal³, Saima Qadeer¹, Asma Ashraf¹, Abdullah Abdul Rehman¹, Misbah Kausar¹, Tabinda Waheed¹ and Afza Arif¹

¹Division of Science and Technology, Department of Zoology, University of Education, Lahore, Pakistan

²Division of Science and Technology, Department of Botany, University of Education, Lahore, Pakistan

³Department of Zoology, The Islamia University of Bahawalpur, Punjab, Pakistan

*Corresponding author: muhammad.asad@ue.edu.pk

Abstract

The proposal is to be the spearhead of adaptive drug development through Evolutionary Medicine and examine the implication of biological ideas in drug manufacturing. There's a kinetic aspect to traditional drug development; this is by definition a continual biological focus, but rapidly emerging diseases such as cancer and bacterial infection almost always do so. Consequently, adaptive medication research treats diseases and their mechanisms as dynamic and formulates effective disease adaptation prediction and combating strategies according to evolutionary principles. One key part of this strategy consists of evolutionary health care, exploring the evolutionary origins of disease and exploiting such understanding to produce more effective medicines. However, adaptive drug development focuses on developing drugs that can accommodate diseases or attack the fundamentally unshakable life routes, concerning how diseases and cells will respond to treatment strain. A more adaptive treatment creation process comes from an evolutionary algorithm, forecasting, and continual tracking of disease development. Two actions are proposed as 'conventional' and 'adaptive' drug development and compared, to show that while formal strategies have paid off on the 'medical progress' side, they created 'resistance to pharmaceuticals', especially of fast-mutating disorders. Adaptive techniques can potentially consider disease progress from initial onset through combination, personalized, and proactive medication design approaches aimed at combatting resilience. In addition, evolutionary medicine answers how present-day healthcare problems such as antimicrobial resistance, obesity, and allergic illnesses result from mismatches between human development and today's environments. Evolutionary theories used in the design of medication both help prevent drug resistance and add new modes of controlling tough conditions like cancer and infections. Adaptive drug development is a dramatic step forward from current medicine, utilizing natural selection and modification to drive the process. Longer-lasting and more successful treatments for changing diseases underscore the importance of an evolutionary perspective in facing modern and future healthcare problems.

Keywords: Drug resistance, Disease resistance, Disease tolerance, Evolutionary medicine, Adaptations, Infection prevention and control

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Introduction

Overview

A new strategy for adaptive drug discovery is to reduce the limits of conventional drug discovery through the use of habituation and evolutionary concepts (Sliwoski et al., 2014). In the conventional paradigm medicine development is approached linearly to deliver medicines for specific disease indications (Moffat et al., 2017). However, the changing character of ailments, especially those activated by fast-spreading viruses or cancer cells, poses a great obstacle, even so (Liao, 2006). Adaptive drug discovery is based on the different dynamics of biological networks for an upgraded adaptive and progressive approach (Eichler et al., 2015). This action approach is founded on an important foundation: the field of evolutionary medicine, which enrolls biological ideas in the analysis of these underlying factors and prognosis. The action plan may allow the experts to design medicines that are productive plus inattentive to coaching given that illnesses change and readjust and due to this likelihood, such action offers a unique change in current health care (Bustin & Jellinger, 2023).

The Conventional Drug Finding Method vs. Adaptive Methods

Figure 1 shows the conventional drug discovery methodology which is usually sequential and time-consuming, starting with target ID, going through drug assessment, optimization, and clinical testing on the way to regulatory clearance (Sinha & Vohora, 2018). This procedure assumes that the disease or biological target does not change throughout research and therapy (Smolen et al., 2014). Though this approach has secured many medical milestones, it is severely limited in its ability to cope with the rapidly changing organisms that cause infectious diseases such as bacteria, viruses and cancer. Standard medications that are taken for granted have proved useless in these instances because the illness mutates and builds immunity (Dickey et al., 2017). In contrast, adaptive methods to drug discoveries account for the progression of diseases

and anticipate how infections or tumor cells will progress with time (Vasan et al., 2019). If these ideas are taken into evolutionary thinking from the start these medicines can grow with the diseases and can face core mechanisms that are not so likely to change (Bizzarri et al., 2020). Being a modern technique, adaptive drug development utilizes evolutionary algorithms, real-time monitoring of the sickness progression as well as predictive modeling of tolerance motifs (Mitra et al., 2022). Therefore, adaptive drug development is becoming increasingly flexible and viable (Laxminarayan et al., 2013).

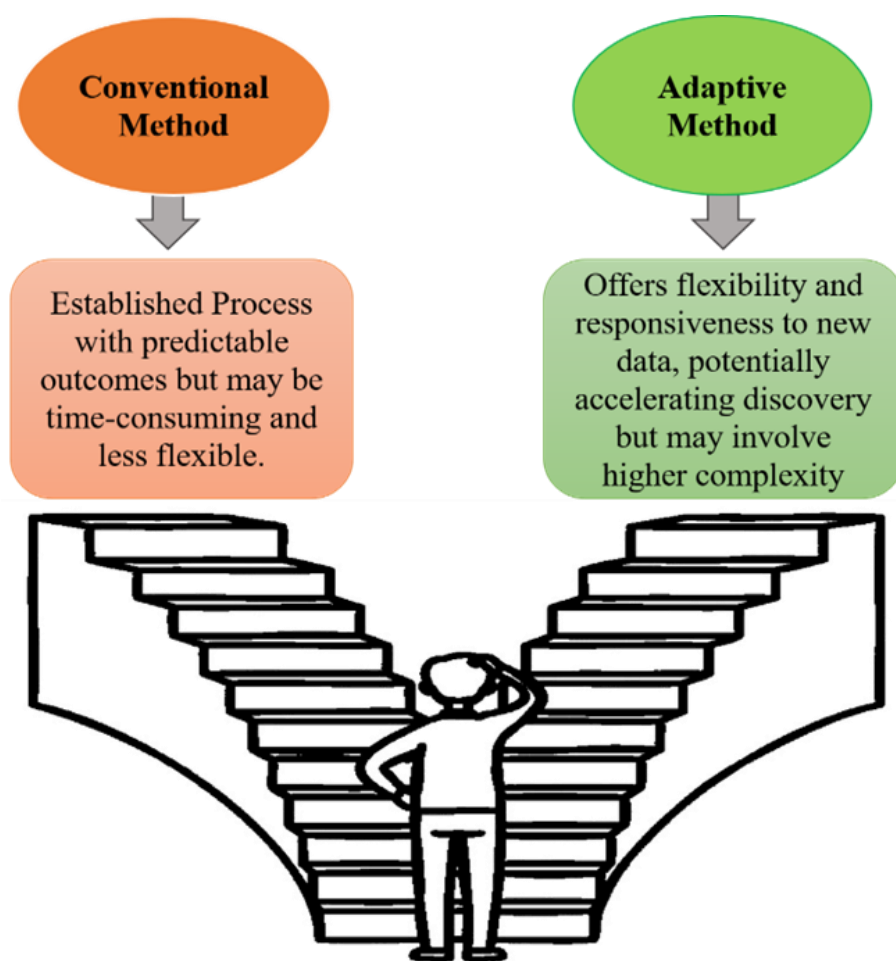


Fig. 1: The Conventional Drug Finding Method Vs the Adaptive Method.

Introduction to Evolutionary Medicine

Evolutionary medicine (Stearns & Medzhitov, 2024) applies evolutionary ideas to a fuller understanding of the roots, development, and therapy of illness. An example of such a book is how it explains how natural selection, genetic drift and mutation shaped the physique of humans and their reaction to sickness (Pigliucci & Kaplan, 2010). The idea that evolution throws light on why certain diseases are out there, how human beings have come to cope with them, and how conventional health care comes up short is the way evolutionary medicine sees health, by looking at it through the prism of evolution. This viewpoint serves to bridge the gap between biological science and medical care, providing novel ways to assess, avoid, and therapy (Gluckman et al., 2016).

Key Principles of Evolutionary Medicine

At its basis, natural healthcare is based on three fundamental ideas. One of the most fundamental is the concept of ecological imbalance, which happens when humans' contemporary environments change significantly from those in which they emerged (McMichael, 2001). Many contemporary health concerns, including overweight, Type 2 diabetes, and heart attacks, can be linked back to this inconsistency, as our physiques have evolved to fit habits that don't meet our current environment (French, 2006). An additional concept is the balance that exists between evolutionary adaptations (Hochachka & Somero, 2002). For example, attributes that were initially useful in old times (like their capacity to preserve fat throughout periods of starvation) are now esteemed as drawbacks in present-day situations where food is copious (Wang et al., 2006). Moreover, ecological medicine allows for the impact of genetic diversity, as natural selection a few times fails to remove deleterious alterations, causing populations with hereditary vulnerability to certain diseases (Hendry et al., 2011).

Relevance to Human Health and Disease

Evolutionary medicine is supremely relevant to understanding and tackling the major health problems of today (Wallace, 2005). Clinicians who understand how our evolutionary past shapes illness vulnerability can design more custom-made safeguards and therapeutic measures

(Kohrt et al., 2020). For instance, the fact that modern cultures experience an elevated incidence of autoimmunity could be laid at the feet of the so-called 'hygiene hypothesis,' that is, our defenses have become better at protecting against a broader category of infectious agents than we have in our modern world, and so, when we live in cleaner environments, we have an overly reactive immune system (Lichtenberger, 2023). Likewise, knowing the biological reasons of aging, fertility and mental health can bring about more customized and viable treatment alternatives (Rechel et al., 2009).

In particular, evolutionary concepts are important in treating drug resistance because they predict how bacteria, viruses and cancer cells may evolve in response to treatment and thus guide the design of adaptive therapeutics (Hughes & Andersson, 2015). This deeper evolutionary framework not only enhances our knowledge of illnesses but also aids in the prediction of upcoming medical issues (Stearns & Nesse, 2010).

Historical Background

Pioneer Strategies in Drug Discovery

The pursuit of drugs has been around for several thousand decades, starting with the adoption of organic treatments that originate from plants, minerals, and animal products (Kuralkar & Kuralkar, 2021). Early medication discovery relied heavily on experiments and failures, with historical civilizations such as the Egyptians, Greeks, and Chinese exploring plants and organic compounds to heal diseases (Sneader, 2005). For decades, this pragmatic strategy for healthcare limited rigorous science but laid the groundwork for subsequent advances (Hannes & Lockwood, 2011). The invention of penicillin in 1928 constituted a watershed moment as shown in figure 2, introducing the idea of antibiotics and sparking the initial concerted attempts to create medications that focused on microbes that caused illness (Wilson & HoIn, 2023). In the mid-twentieth century, the emergence of synthetic chemicals enabled researchers to produce pharmaceuticals in the lab, paving the way for the focused development of medicines and the potential to treat a larger spectrum of disorders (Greenwood, 2008).

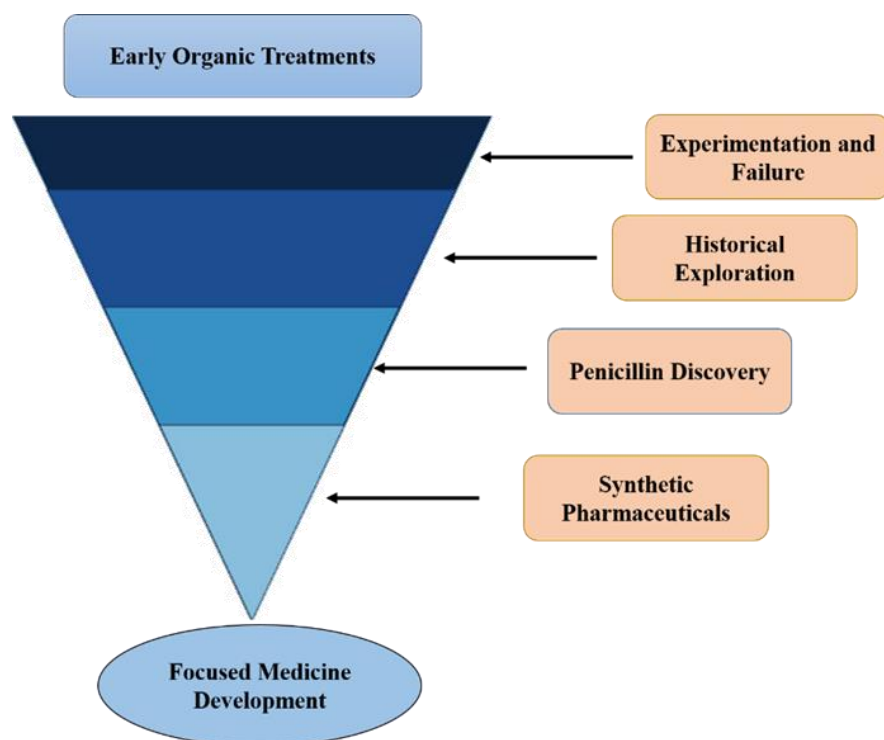


Fig. 2: Shows the Evolutionary Discovery of Medicine.

Milestones in Adaptive Strategies

With further research forward in medicine, it became apparent that ailments especially those driven by infections or cells that progress into cancer were able to adapt and selectively evolve drug resistance (Vasan et al., 2019). Implementing progressive tactics in the study of drugs is due to this difficulty (Heifetz et al., 2009). The introduction of combined therapies (which involve several treatments that may work to hinder obstruction from occurring) was another example of being noteworthy breakthrough. This action approach was very fruitful in addressing diseases like HIV and TB.

One other important revolution was the emergence of customized medicine, which permits more targeted treatments based on a patient's genetic and biochemical contour, often targeting the evolutionary route of illness development. Adaptive techniques have lately begun to incorporate evolutionary ideas, including designing medications that anticipate new pathogen alterations, which aids in their efficacy over the long run (Carroll et al., 2014). These significant developments show an advancement in the creation of medications towards quicker and more responsive strategies that tackle the dynamic character of the illness (Desai, 2012).

The Rise of Evolutionary Medicine

Key Developments in Understanding Evolutionary Influences on Disease

Evolutionary healthcare has emerged as a result of increasing awareness of how evolutionary processes impact the biology of illnesses

(Stearns & Medzhitov, 2024). In the first decades of the twentieth century, experts such as Charles Darwin and Alfred Russel Wallace set the framework for the notion of organic choosing, which was eventually employed in human health. Yet it did not include as long as the late twentieth century that the study of evolution was introduced into medical studies.

Key advances in this subject involve an improved awareness of historical imbalances, which occur when contemporary living variables collide with the human body's natural modifications resulting in disorders like weight gain, diabetes, and heart difficulties. A further important field has been the investigation of pathogen evolution, especially in the context of antimicrobial resistance, which has revealed that bacteria and viruses adapt rapidly to medication challenges, necessitating novel treatment options.

Remarkable Achievements and Triumphs

Several developments have emphasized the significance of evolutionary medicine in current healthcare (Stearns & Medzhitov, 2024). One of the field's most significant achievements was the finding of antimicrobial resistance, which illustrated how bacteria can change to render previously successful drugs worthless (Levy, 2013). This resulted in a higher priority on studying microbial evolution and creating novel techniques to combat resilience (Philippot & Griffiths, 2021). Oncologists have used evolutionary ideas to combat tumors, resulting in the creation of adaptable treatments that target tumor evolutionary paths (Gatenby & Brown, 2020).

Dr. Paul Ewald and Dr. Randolph Nesse have advanced the knowledge of medical evolution by investigating how evolutionary pressures have impacted human health, which has implications for the medical management of infectious illnesses, psychological issues, and persistent illnesses. These contributions have not only shed light on the causes of illness but have also sparked new methods of disease management in medical settings (Lupton, 2012).

Concept of Adaptive Drug Discovery

Mechanisms of Adaptation (genetic, environmental, etc.)

Adaptation in biology applies to how organisms adjust to changes in their environment or genetic composition as a means to live and propagate (Brandon, 2014). Mutations, natural selection, and genetic drift all contribute to genetic modification, which happens when advantageous features grow more prevalent in a population over centuries (Lynch et al., 2016).

Environmental adjustment occurs when organisms react to abrupt shifts in their such as shifts in temperature or access to resources (Wingfield et al., 2011). These factors, whether genetic or environmental, affect animals' evolutionary routes, allowing them to thrive in shifting circumstances (Grime & Pierce, 2012). Bacteria, for instance, may adapt to antibiotics by genetic mutations conferring obstruction, whereas humans have adjusted to nutritional changes over millennia (Bartell et al., 2019).

How Biological Adaptation Informs Drug Design

Knowing how organisms evolve is critical for drug design, especially in tackling rapidly evolving diseases like bacterial infections and malignancies (Brown & Wright, 2016). Drug makers use lessons from natural selection to anticipate how diseases may respond to therapies (Al-Lazikani et al., 2012). Scientists can build longer-lasting medicines by targeting pathways that are less prone to mutate or developing pharmaceuticals that may change with diseases (Melo et al., 2011). For example, conjunction medicines are intended to lessen the risk of tolerance by addressing numerous targets at the same time, making it more difficult for the illness to adapt (Wen et al., 2015). This comprehension of adaptation operates innovation in medicinal makeup, allowing researchers to predict and outmaneuver ailment biological habituation.

Challenges in Traditional Drug Discovery

Adaptation to Drugs (e.g., antibiotics, cancer treatments)

One of the major obstacles associated with traditional drug discovery is the emergence of drug resistance, particularly concerning antibiotics and cancer treatments (Muteeb et al., 2023). Pathogens and cancer cells have the natural latent to adapt under evolutionary pressure, often resulting in changes that leave treatments fruitless (Aktipis & Nesse, 2013). Antibiotic abuse and exploitation, for example, have optimized the evolution of resistance in bacteria, resulting in the turning up of difficult-to-treat superbugs. Furthermore, cancer cells can develop approaches to withstand chemotherapy, resulting in defeated therapy and development of the disease. These difficulties underscore traditional drug discovery's limitations, which often fail to adjust for disease dynamics and evolution (Field et al., 2017).

Significance of Adaptive Approaches for Overcoming Resistance

The need to combat medication resistance has created a need for adaptive techniques. Their goal is to create medicines that account for possibility of evolution during disease (Stearns & Medzhitov, 2024). For example, adaptive methods can include combination therapies where multiple drugs are used to strike several different pathways, and the developing of drugs that can change in real time based on changes in the disease (Al-Lazikani et al., 2012). Anticipating how disease may evolve in the context of therapy enables it to develop more robust medicines. For example, standard one-size-fits-all techniques for therapy of cancer have already been outpaced by adaptive medicines that adapt to the tumor's evolutionary changes through treatment.

Incorporating Evolutionary Concepts in Drug Discovery

Evolutionary Demands and Drug Resilience

The emergence of drug resilience mediated by evolutionary pressures, such as selective assault by medication therapy (Konner, 2007), are critical. If we can deliver a medicine directly at a specific part of a pathogen or a cancer cell, then every cell in the vicinity that can evade the treatment will survive and continue to replicate (Ben Jacob et al., 2012). However, this selection mechanism forces the disease to become less

and less treatable as time goes by. By understanding these evolutionary pressures, researchers can design treatments that either decrease the likelihood of resistance, or zero in on genetic defects in the disease (Baym et al., 2016).

Using Evolutionary Biology to Predict Pathogen or Tumor Modifications

Integrating biological evolution into the search for drugs enables scientists to predict how diseases such as cancer or infectious viruses may evolve (Gatenby & Brown, 2020). This foresight is critical for developing medications that are nevertheless successful notwithstanding the disease's evolutionary changes. Scientists can detect probable mutations that might give rise to tolerance by modeling how tumors or pathogens evolve, and then create medications that either avoid or retain effective against those changes. Forecasting evolutionary frameworks are currently being employed to direct the creation of next-generation medications that can keep up with disease progression.

Evolutionary Medicine: A Framework for Innovation

Using Evolutionary Concept in Medicine

In essence, we blame evolutionary theory as the basis for identifying the reasons those diseases arose, with possible solutions (Dethlefsen et al., 2007). Evolutionary medicine illuminates the 'why?' by documenting how natural selection, adaption, and genetic variation affect human health; and the 'how?' by exploring the 'survival of the sick' (Gluckman et al., 2012) and looking to fight illness through an evolutionary lens (Benton et al., 2021). Creating drug obstructions is explained in the naturalistic battle between humans and pathogens; the concept of progressive imbalance has contributed to the development of persistent illnesses like diabetes, which occur when there is an imbalance between a person's way of life to date and the natural surroundings a person's organs are functional on.

Case Reports for Malaria, Cancer, and Antibiotic Resistance

Evolutionary therapy has led to the development of breakthrough ways of treating diseases like malaria, cancer and antibiotic susceptibility (Ahmed et al., 2023). Evolutionary concepts have been behind the creation of mixed drugs in malaria, in which keeping the parasite from becoming resistant is the idea. Utilizing evolutionary concepts, cancer has been regarded as one of the most significant worldwide health problems and has been tackled to lessen the amount of resistance emergence by way of selective antibiotic consumption and medication development that attacks evolutionary susceptible elements in bacteria (Sinha et al., 2014).

Advantages of Evolutionary Medicine in Drug Discovery

Designing Drugs for Evolutionary Resilience

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Medications Tailored to Pathogen Evolutionary Dynamics

Better and more lasting treatments are those that are adapted to pathogen patterns of evolution (Didelot et al., 2016). To catch up to the host response to the ever-changing disease, physicians can recognize pathways of infection proliferation and adjust the medication in real-time (Zhu et al., 2014). Specifically, this method is thought to be very effective with cancer since the fast growth of tumor cells often hinders treatment (He et al., 2022). By avoiding these changes in the cancer cells, adaptive medicines that monitor and inhibit these changes can improve patient results (Vasan et al., 2019).

Tools and Techniques in Adaptive Drug Discovery

Scientific Breakthroughs

The adaptive search for drugs has been transformed through scientific advances. Now, due to genomics, biology, and computer modeling, researchers can analyze pathogen genetics and predict how they will evolve (Mitra et al., 2022). These technologies can enable the ability to manipulate disease networks and identify potential resistance variants early (Mores et al., 2021). For example, a numerical model simulates a pathogen, or tumor, that will respond to different drugs, resulting in the creation of improved therapies.

Application of Evolutionary Approaches in Drug Architecture

Natural selection has started to influence the development of evolutionary computational algorithms for drug design. These algorithms mimic the process of evolution, by generating and evaluating a large number of drug prospects looking for the ones carrying the most promising therapeutic qualities (Lambrinidis & TsantiliKakoulidou, 2021). These rely on the mechanisms of evolution to find chemicals that are both successful and resilient to building resistance (Le & Winkler, 2016). This technique also accelerates the discovery of which medications are vulnerable to changing disease environments.

Drug Adaptation and Evolving Healthcare

Understanding Evolutionary Networks of Drug Resilience

Efficient treatments are thus devised to understand the evolutionary processes that are responsible for medication resistance (Andersson

et al., 2020). By studying the genetic and environmental variables that trigger resistance, scientists can locate particular changes or adjustments that permit infections and cancer cells to elude treatment (Marine et al., 2020). Having such information helps us work out how we can create medications that either avoid or still work potently even in the presence of these alterations.

Approaches for Delaying or Preventing Resistance Advancement

According to Medical Evolution, some measures are suggested such as the use of a mix of medications in an attempt to reduce the effect of the selective pressure and the creation of the planes of action aimed at the alternative pathways at the same time (Baym et al., 2016). Second, making the disease less able to change to therapy is a way to keep the odds of resistance down (Bergers & Hanahan, 2008). Furthermore, if doctors follow evolutionary knowledge, they can predict which structures of patients under therapy will be antagonistic and adjust interventions such that the probability of resistance being created is reduced (Andersson et al 2020).

Drug Discovery using Evolutionary Guidelines

Following are few important evolutionary guidelines regarding discovery of drug as shown in figure 3.

Study of Antibiotic Formulation Using Evolutionary Perspectives

Evolutionary ideas have been applied to design antibiotics, mitigating the effect of resistance, using less resistant designs (Andersson et al., 2020). The highly preserved bacterial activities that are difficult to alter are addressed with successful resistance decreases (Hurdle et al., 2011). By focusing on evolutionary faults, scientists have devised new categories of antibiotics that are better than bacterial adaptability (Levy, 2013).

Focussing on Extremely Preserved Biological Mechanisms

An effective drug design method addresses highly resilient biological pathways that are the same and important across many species (Meanwell, 2016). These systems are more difficult to change, making medications aimed at them more likely to be efficient as the years pass. The conventional approaches may fail because of tolerance; that's where this method comes in handy to discover medicines for fast-changing diseases.

Case Studies in Adaptive Drug Discovery

Evolutionary approaches to the current healthcare antimicrobial resistance problem (Jindal et al., 2015) offer unique solutions to the problem. Studying how bacteria become resistant and designing drugs to counter evolutionary weaknesses has led scientists to develop medicines to slow the growth of resistant strains (Mantravadi et al., 2019).

Vaccine and Immune System Escape

Adaptive vaccinations that keep up with the fast mutation of diseases such as viruses (developing) are becoming more important (Gandon & Lion, 2022). But by forecasting how a virus might mutate to escape the immune system, researchers can create potent vaccinations against a lot of strains of the virus. Developing vaccines for often evolving viruses such as influenza and COVID-19 (Dos Santos, 2021) has this technique organized very well.

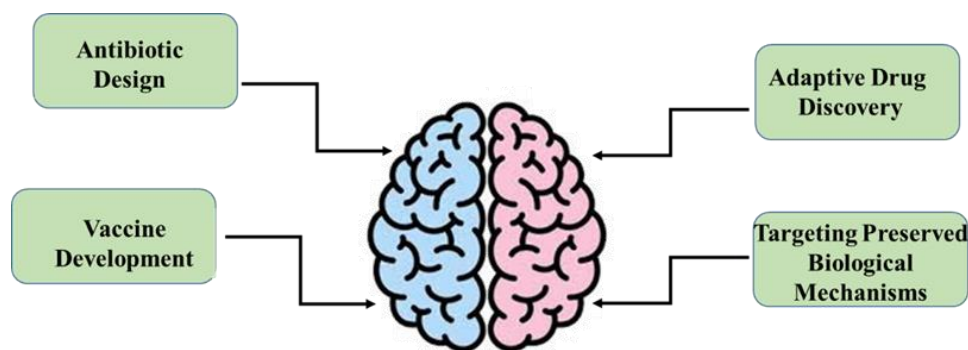


Fig. 3: shows the outlook of evolutionary guidelines for drug discovery.

Difficulties and Moral Attention

Moral Aspects of Evolutionary Drug Investigation

Evolutionary ideas are in demand in drug development for different ethical issues, particularly regarding bringing development in line with the proper use of medicines (Carroll et al., 2014). Take for example creating medications using these methods could lead to their abuse, which would cause a more rapid development of resistance they were meant to avoid (Holmes et al., 2016).

Conclusion

Adaptive drug development, based on the principles of evolutionary medicine, offers a revolutionary approach to addressing contemporary healthcare challenges. In contrast to conventional drug development, which frequently struggles to match the fast-changing nature of diseases, adaptive strategies view disease progression as an evolving process that demands ongoing prediction, personalization, and flexibility.

Integrating evolutionary theory into drug design not only enhances treatment effectiveness but also facilitates the combat against the growing challenge of drug resistance in infections and cancers. Adaptive techniques focus on individualized treatment, sustained resilience, and anticipatory measures that correspond with the evolutionary roots of illness. This change in perspective not only alters our approach to treatment but also establishes adaptive drug development as an essential advancement in addressing present and upcoming health challenges

References

- Ahmed, S., Ahmed, M. Z., Rafique, S., Almasoudi, S. E., Shah, M., Jalil, N. A. C., & Ojha, S. C. (2023). Recent approaches for downplaying antibiotic resistance: Molecular mechanisms. *BioMed Research International*, 2023(1), 5250040. <https://doi.org/10.1155/2023/5250040>
- Aktipis, C. A., & Nesse, R. M. (2013). Evolutionary foundations for cancer biology. *Evolutionary Applications*, 6(1), 144–159. <https://doi.org/10.1111/eva.12034>
- Al-Lazikani, B., Banerji, U., & Workman, P. (2012). Combinatorial drug therapy for cancer in the post-genomic era. *Nature Biotechnology*, 30(7), 679–692. <https://doi.org/10.1038/nbt.2284>
- Andersson, D. I., Balaban, N. Q., Baquero, F., Courvalin, P., Glaser, P., Gophna, U., & Tønjum, T. (2020). Antibiotic resistance: Turning evolutionary principles into clinical reality. *FEMS Microbiology Reviews*, 44(2), 171–188. <https://doi.org/10.1093/femsre/fuaa001>
- Bartell, J. A., Sommer, L. M., Haagenen, J. A. J., Loch, A., Espinosa, R., Molin, S., & Johansen, H. K. (2019). Evolutionary highways to persistent bacterial infection. *Nature Communications*, 10(1), 629. <https://doi.org/10.1038/s41467-019-08463-9>
- Baym, M., Stone, L. K., & Kishony, R. (2016). Multidrug evolutionary strategies to reverse antibiotic resistance. *Science*, 351(6268), aad3292. <https://doi.org/10.1126/science.aad3292>
- Ben-Jacob, E., Coffey, D. S., & Levine, H. (2012). Bacterial survival strategies suggest rethinking cancer cooperativity. *Trends in Microbiology*, 20(9), 403–410. <https://doi.org/10.1016/j.tim.2012.06.005>
- Benton, M. L., Abraham, A., LaBella, A. L., Abbot, P., Rokas, A., & Capra, J. A. (2021). The influence of evolutionary history on human health and disease. *Nature Reviews Genetics*, 22(5), 269–283. <https://doi.org/10.1038/s41576-020-00305-9>
- Bergers, G., & Hanahan, D. (2008). Modes of resistance to anti-angiogenic therapy. *Nature Reviews Cancer*, 8(8), 592–603. <https://doi.org/10.1038/nrc2442>
- Bizzarri, M., Minini, M., & Monti, N. (2020). Revisiting the concept of human disease: Rethinking the causality concept in pathogenesis for establishing a different pharmacological strategy. In *Approaching Complex Diseases: Network-Based Pharmacology and Systems Approach in Bio-Medicine* (pp. 1–34). Springer. https://doi.org/10.1007/978-3-030-41239-6_1
- Brandon, R. N. (2014). *Adaptation and environment* (Vol. 1040). Princeton University Press.
- Brown, E. D., & Wright, G. D. (2016). Antibacterial drug discovery in the resistance era. *Nature*, 529(7586), 336–343. <https://doi.org/10.1038/nature17042>
- Bustin, S. A., & Jellinger, K. A. (2023). Advances in molecular medicine: Unravelling disease complexity and pioneering precision healthcare. *International Journal of Molecular Sciences*, 24(18), 14168. <https://doi.org/10.3390/ijms241814168>
- Carroll, S. P., Jørgensen, P. S., Kinnison, M. T., Bergstrom, C. T., Denison, R. F., Gluckman, P., & Tabashnik, B. E. (2014). Applying evolutionary biology to address global challenges. *Science*, 346(6207), 1245993. <https://doi.org/10.1126/science.1245993>
- Desai, N. (2012). Challenges in development of nanoparticle-based therapeutics. *The AAPS Journal*, 14(2), 282–295. <https://doi.org/10.1208/s12248-012-9339-4>
- Dethlefsen, L., McFall-Ngai, M., & Relman, D. A. (2007). An ecological and evolutionary perspective on human–microbe mutualism and disease. *Nature*, 449(7164), 811–818. <https://doi.org/10.1038/nature06245>
- Dickey, S. W., Cheung, G. Y. C., & Otto, M. (2017). Different drugs for bad bugs: Antivirulence strategies in the age of antibiotic resistance. *Nature Reviews Drug Discovery*, 16(7), 457–471. <https://doi.org/10.1038/nrd.2017.23>
- Didelot, X., Walker, A. S., Peto, T. E., Crook, D. W., & Wilson, D. J. (2016). Within-host evolution of bacterial pathogens. *Nature Reviews Microbiology*, 14(3), 150–162. <https://doi.org/10.1038/nrmicro.2015.13>
- Dos Santos, W. G. (2021). Impact of virus genetic variability and host immunity for the success of COVID-19 vaccines. *Biomedicine & Pharmacotherapy*, 136, 111272. <https://doi.org/10.1016/j.biopha.2021.111272>
- Eichler, H. G., Baird, L. G., Barker, R., Bloechl-Daum, B., Børsum-Kristensen, F., Brown, J., & Hirsch, G. (2015). From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. *Clinical Pharmacology & Therapeutics*, 97(3), 234–246. <https://doi.org/10.1002/cpt.59>
- Field, M. C., Horn, D., Fairlamb, A. H., Ferguson, M. A. J., Gray, D. W., Read, K. D., ... & Gilbert, I. H. (2017). Anti-trypanosomatid drug discovery: An ongoing challenge and a continuing need. *Nature Reviews Microbiology*, 15(4), 217–231. <https://doi.org/10.1038/nrmicro.2016.193>
- French, V. (2006). Connecting health concepts and health behavior: The construction of health identity. (*Additional publication info needed: journal/book title, volume, publisher—please provide if available.*)
- Gandon, S., & Lion, S. (2022). Targeted vaccination and the speed of SARS-CoV-2 adaptation. *Proceedings of the National Academy of Sciences*, 119(3), e2110666119. <https://doi.org/10.1073/pnas.2110666119>
- Gatenby, R. A., & Brown, J. S. (2020). Integrating evolutionary dynamics into cancer therapy. *Nature Reviews Clinical Oncology*, 17(11), 675–686. <https://doi.org/10.1038/s41571-020-0413-5>
- Gluckman, P., Beedle, A., Buklijas, T., Low, F., & Hanson, M. (2016). *Principles of evolutionary medicine*. Oxford University Press.
- Greenwood, D. (2008). *Antimicrobial drugs: Chronicle of a twentieth century medical triumph*. Oxford University Press.
- Grime, J. P., & Pierce, S. (2012). *The evolutionary strategies that shape ecosystems*. John Wiley & Sons.
- Hannes, K., & Lockwood, C. (2011). Pragmatism as the philosophical foundation for the Joanna Briggs meta-aggregative approach to qualitative evidence synthesis. *Journal of Advanced Nursing*, 67(7), 1632–1642. <https://doi.org/10.1111/j.1365-2648.2011.05659.x>

- He, W., Li, Q., Lu, Y., Ju, D., Gu, Y., Zhao, K., & Dong, C. (2022). Cancer treatment evolution from traditional methods to stem cells and gene therapy. *Current Gene Therapy*, 22(5), 368–385. <https://doi.org/10.2174/1566523222666220516140048>
- Heifetz, R. A., Grashow, A., & Linsky, M. (2009). *The practice of adaptive leadership: Tools and tactics for changing your organization and the world*. Harvard Business Press.
- Hendry, A. P., Kinnison, M. T., Heino, M., Day, T., Smith, T. B., Fitt, G., & Carroll, S. P. (2011). Evolutionary principles and their practical application. *Evolutionary Applications*, 4(2), 159–183. <https://doi.org/10.1111/j.1752-4571.2010.00165.x>
- Hochachka, P. W., & Somero, G. N. (2002). *Biochemical adaptation: Mechanism and process in physiological evolution*. Oxford University Press.
- Holmes, A. H., Moore, L. S. P., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., & Piddock, L. J. V. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet*, 387(10014), 176–187. [https://doi.org/10.1016/S0140-6736\(15\)00473-0](https://doi.org/10.1016/S0140-6736(15)00473-0)
- Hughes, D., & Andersson, D. I. (2015). Evolutionary consequences of drug resistance: Shared principles across diverse targets and organisms. *Nature Reviews Genetics*, 16(8), 459–471. <https://doi.org/10.1038/nrg3922>
- Hurdle, J. G., O'Neill, A. J., Chopra, I., & Lee, R. E. (2011). Targeting bacterial membrane function: An underexploited mechanism for treating persistent infections. *Nature Reviews Microbiology*, 9(1), 62–75. <https://doi.org/10.1038/nrmicro2474>
- Jindal, A. K., Pandya, K., & Khan, I. D. (2015). Antimicrobial resistance: A public health challenge. *Medical Journal Armed Forces India*, 71(2), 178–181. <https://doi.org/10.1016/j.mjafi.2014.09.011>
- Kohrt, B. A., Ottman, K., Panter-Brick, C., Konner, M., & Patel, V. (2020). Why we heal: The evolution of psychological healing and implications for global mental health. *Clinical Psychology Review*, 82, 101920. <https://doi.org/10.1016/j.cpr.2020.101920>
- Konner, M. (2007). Trauma, adaptation, and resilience: A cross-cultural and evolutionary perspective. In *Understanding trauma: Biological, psychological and cultural perspectives* (pp. 300–338). Cambridge University Press.
- Kuralkar, P., & Kuralkar, S. V. (2021). Role of herbal products in animal production—An updated review. *Journal of Ethnopharmacology*, 278, 114246. <https://doi.org/10.1016/j.jep.2021.114246>
- Lambrinidis, G., & Tsantili-Kakoulidou, A. (2021). Multi-objective optimization methods in novel drug design. *Expert Opinion on Drug Discovery*, 16(6), 647–658. <https://doi.org/10.1080/17460441.2021.1888022>
- Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K. M., Wertheim, H. F. L., Sumpradit, N., & Cars, O. (2013). Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases*, 13(12), 1057–1098. [https://doi.org/10.1016/S1473-3099\(13\)70318-9](https://doi.org/10.1016/S1473-3099(13)70318-9)
- Le, T. C., & Winkler, D. A. (2016). Discovery and optimization of materials using evolutionary approaches. *Chemical Reviews*, 116(10), 6107–6132. <https://doi.org/10.1021/acs.chemrev.5b00560>
- Levy, S. B. (2013). *The antibiotic paradox: How miracle drugs are destroying the miracle* (2nd ed.). Springer.
- Liao, J. B. (2006). Cancer issue: Viruses and human cancer. *The Yale Journal of Biology and Medicine*, 79(3–4), 115–122.
- Lichtenberger, F. (2023). *Allergic to life: How the human body rejects the modern world*. Springer Nature.
- Lupton, D. (2012). *Medicine as culture: Illness, disease and the body* (3rd ed.). SAGE Publications.
- Lynch, M., Ackerman, M. S., Gout, J. F., Long, H., Sung, W., Thomas, W. K., & Foster, P. L. (2016). Genetic drift, selection and the evolution of the mutation rate. *Nature Reviews Genetics*, 17(11), 704–714. <https://doi.org/10.1038/nrg.2016.104>
- Mantravadi, P. K., Kalesh, K. A., Dobson, R. C., Hudson, A. O., & Parthasarathy, A. (2019). The quest for novel antimicrobial compounds: Emerging trends in research, development, and technologies. *Antibiotics*, 8(1), 8. <https://doi.org/10.3390/antibiotics8010008>
- Marine, J. C., Dawson, S. J., & Dawson, M. A. (2020). Non-genetic mechanisms of therapeutic resistance in cancer. *Nature Reviews Cancer*, 20(12), 743–756. <https://doi.org/10.1038/s41568-020-00310-0>
- McMichael, A. J. (2001). *Human frontiers, environments and disease: Past patterns, uncertain futures*. Cambridge University Press.
- Meanwell, N. A. (2016). Improving drug design: An update on recent applications of efficiency metrics, strategies for replacing problematic elements, and compounds in nontraditional drug space. *Chemical Research in Toxicology*, 29(4), 564–616. <https://doi.org/10.1021/acs.chemrestox.6b00088>
- Melo, A., Monteiro, L., Lima, R. M., de Oliveira, D. M., de Cerqueira, M. D., & El-Bachá, R. S. (2011). Oxidative stress in neurodegenerative diseases: Mechanisms and therapeutic perspectives. *Oxidative Medicine and Cellular Longevity*, 2011(1), 467180. <https://doi.org/10.1155/2011/467180>
- Mitra, D., Mitra, D., Bensaad, M. S., Sinha, S., Pant, K., Pant, M., & Mohapatra, P. K. D. (2022). Evolution of bioinformatics and its impact on modern bioscience in the twenty-first century: Special attention to pharmacology, plant science and drug discovery. *Computational Toxicology*, 24, 100248. <https://doi.org/10.1016/j.comtox.2022.100248>
- Moffat, J. G., Vincent, F., Lee, J. A., Eder, J., & Prunotto, M. (2017). Opportunities and challenges in phenotypic drug discovery: An industry perspective. *Nature Reviews Drug Discovery*, 16(8), 531–543. <https://doi.org/10.1038/nrd.2017.111>
- Mores, A., Borrelli, G. M., Laidò, G., Petruzzino, G., Pecchioni, N., Amoroso, L. G. M., & Marone, D. (2021). Genomic approaches to identify molecular bases of crop resistance to diseases and to develop future breeding strategies. *International Journal of Molecular Sciences*, 22(11), 5423. <https://doi.org/10.3390/ijms22115423>
- Muteeb, G., Rehman, M. T., Shahwan, M., & Aatif, M. (2023). Origin of antibiotics and antibiotic resistance, and their impacts on drug development: A narrative review. *Pharmaceuticals*, 16(11), 1615. <https://doi.org/10.3390/ph16111615>
- Nesse, R. M., Bergstrom, C. T., Ellison, P. T., Flier, J. S., Gluckman, P., Govindaraju, D. R., & Valle, D. (2010). Making evolutionary biology a basic science for medicine. *Proceedings of the National Academy of Sciences*, 107(Suppl. 1), 1800–1807. <https://doi.org/10.1073/pnas.0914475107>
- Philippot, L., Griffiths, B. S., & Langenheder, S. (2021). Microbial community resilience across ecosystems and multiple disturbances. *Microbiology and Molecular Biology Reviews*, 85(2), e00112–20. <https://doi.org/10.1128/MMBR.00112-20>
- Pigliucci, M., & Kaplan, J. (2010). *Making sense of evolution: The conceptual foundations of evolutionary biology*. University of Chicago Press.

- Rechel, B., Doyle, Y., Grundy, E., & McKee, M. (2009). How can health systems respond to population ageing? *World Health Organization*, 2009(1), 1–24.
- Sinha, S., & Vohora, D. (2018). Drug discovery and development: An overview. In *Pharmaceutical Medicine and Translational Clinical Research* (pp. 19–32). Academic Press. <https://doi.org/10.1016/B978-0-12-802103-3.00002-7>
- Sinha, S., Medhi, B., & Sehgal, R. (2014). Challenges of drug-resistant malaria. *Parasite*, 21, 61. <https://doi.org/10.1051/parasite/2014059>
- Sliwoski, G., Kothiwale, S., Meiler, J., & Lowe, E. W. (2014). Computational methods in drug discovery. *Pharmacological Reviews*, 66(1), 334–395. <https://doi.org/10.1124/pr.112.007336>
- Smolen, J. S., Landewé, R., Breedveld, F. C., Buch, M., Burmester, G., Dougados, M., & Van Der Heijde, D. (2014). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Annals of the Rheumatic Diseases*, 73(3), 492–509. <https://doi.org/10.1136/annrheumdis-2013-204573>
- Sneider, W. (2005). *Drug discovery: A history*. John Wiley & Sons.
- Stearns, S. C., & Medzhitov, R. (2024). *Evolutionary medicine* (2nd ed.). Oxford University Press.
- Stearns, S. C., Nesse, R. M., Govindaraju, D. R., & Ellison, P. T. (2010). Evolutionary perspectives on health and medicine. *Proceedings of the National Academy of Sciences*, 107(Suppl. 1), 1691–1695. <https://doi.org/10.1073/pnas.0906187106>
- Vasan, N., Baselga, J., & Hyman, D. M. (2019). A view on drug resistance in cancer. *Nature*, 575(7782), 299–309. <https://doi.org/10.1038/s41586-019-1730-1>
- Wallace, D. C. (2005). A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: A dawn for evolutionary medicine. *Annual Review of Genetics*, 39, 359–407. <https://doi.org/10.1146/annurev.genet.39.110304.095751>
- Wang, T., Hung, C. C., & Randall, D. J. (2006). The comparative physiology of food deprivation: From feast to famine. *Annual Review of Physiology*, 68, 223–251. <https://doi.org/10.1146/annurev.physiol.68.040104.105739>
- Wen, H., Jung, H., & Li, X. (2015). Drug delivery approaches in addressing clinical pharmacology-related issues: Opportunities and challenges. *The AAPS Journal*, 17, 1327–1340. <https://doi.org/10.1208/s12248-015-9795-3>
- Wilson, B. A., & Ho, B. T. (2023). *Revenge of the microbes: How bacterial resistance is undermining the antibiotic miracle* (2nd ed.). John Wiley & Sons.
- Wingfield, J. C., Kelley, J. P., & Angelier, F. (2011). What are extreme environmental conditions and how do organisms cope with them? *Current Zoology*, 57(3), 363–374. <https://doi.org/10.1093/czoolo/57.3.363>
- Zhu, X., Radovic-Moreno, A. F., Wu, J., Langer, R., & Shi, J. (2014). Nanomedicine in the management of microbial infection—overview and perspectives. *Nano Today*, 9(4), 478–498. <https://doi.org/10.1016/j.nantod.2014.07.001>