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# Model Organisms and Systems in Life Sciences

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**ABSTRACT**

Approximately 6-7% of newborns have congenital anomalies. The causes of these anomalies are genetic-based, environmental, or multifactorial. The cause of almost 50% of congenital anomalies is not fully known. There are many specific birth defects as part of the syndromes. Even though the syndromes are complex, they use common signaling pathways in the developmental process. Because of the complex nature of developmental disorders, different types of model systems are necessary to understand the molecular pathogenesis of diseases. The molecular infrastructure of diseases and problems in a developmental process is revealed with different types of model systems. While studying the development of multicellular organisms, related molecular and cellular processes are examined. While conducting these studies, model organisms, organoids, and computerized (in silico) models are used. Each method has its advantages and disadvantages.
In this review, we will provide recent knowledge on the advantages and disadvantages of modeling systems used to understand developmental processes.

**Keywords**: Model organisms, organoids, computerized modeling, in silico modeling, model, organism, biology

# Makalenin Türkçe Başlığı

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**ÖZ**

Yenidoğanların yaklaşık %6-7'sinde konjenital (doğuştan gelen) anomaliler bulunmaktadır. Bu anomalilerin nedenleri genetik, çevresel veya multifaktöriyel olabilir. Konjenital anomalilerin yaklaşık %50'sinin nedeni tam olarak bilinmemektedir. Birçok özgül konjenital anomali sendromların bir parçası olarak bulunmaktadır. Sendromların bulguları karmaşık olmasına rağmen gelişim süreçlerinde ortak sinyal yolaklarını kullanırlar. Gelişimsel bozuklukların karmaşık doğası nedeniyle, hastalıkların moleküler patogenezini anlamak için farklı tipte model sistemlerin kullanılması gerekmektedir. Gelişimsel bir süreçteki hastalık ve problemlerin moleküler temeli, farklı model sistemlerle açıklanmaktadır. Çok hücreli organizmaların gelişimini incelerken, ilişkili moleküler ve hücresel süreçler araştırılır. Bu çalışmalar yapılırken model organizmalar, organoidler ve hesaplamalı (in silico) modeller kullanılmaktadır. Her yöntemin kendine özel avantajları ve dezavantajları bulunmaktadır. Bu derlemede, gelişimsel süreçlerin anlaşılmasında kullanılan model sistemlerin avantajları ve dezavantajları hakkındaki güncel bilgiler sunulmaktadır.



***Anahtar sözcükler:*** Model organizmalar, organoidler, bilgisayarlı modelleme, in silico modelleme, model, organizma, biyoloji

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## Model organisms

Model organisms are useful tools to understand biological and physiological mechanisms.

These are non-human species. The purpose of utilizing model organisms is to produce data, models, and theories that can apply to other organisms, especially those that are somewhat more complex [1]. These organisms are not difficult to grow and maintain in vitro and offer wonderful test benefits. There are many model organisms, and these organisms should be chosen relying upon the motivation behind the research. On the other hand, there are several limitations for researchers like time and money [2]. Despite these disadvantages, model organisms are the cheapest modeling method than alternatives. Unlike mammalian models, *Caenorhabditis elegans*, a nematode, offers to the researchers alternative experimental approaches at lower cost in animal models of invertebrates such as *Drosophila melanogaster* [3]. At the same time, advanced genome manipulation techniques such as RNAi make it possible to model human diseases in these model organisms [4].

Notwithstanding every one of these advantages, the low similarity rate between the human genome and the *C. elegans* genome (40%) and the *D. melanogaster* genome (60%) reduces the success rate in experiments and limits the modeling of many diseases phenotypes in these organisms [5, 6]. Zebrafish (*Danio rerio*) has been utilized throughout the previous 20 years as a novel methodology against *C. elegans* and *D. melanogaster* models. The way that the zebrafish is a vertebrate increase its physiological and anatomical similarity to humans. Also, the high closeness of the human and zebrafish genome (It's nearly 70), makes it possible to model more developmental disorders than the *C.elegans* or D.melanogaster in Zebrafish.

### *Drosophila Melanogaster*

*Drosophila melanogaster*, a fruit fly, is quite possibly the most generally utilized model organism in biological sciences. For over a hundred years, *Drosophila melanogaster* has become a crucial life form for research because of its benefits, such as quick reproductive time. As a result of the development of molecular tools, model organisms have kept pace with the latest developments [7]. The whole-genome mapping of the *D. melanogaster* has been shown that there are around 13600 genes in its genome. Following the completion of the Human Genome Project, it was calculated that 60-65% of human disorders can be modeling in *D.melanogaster* [5, 8].

*Drosophila melanogaster* has been used very widely in biological research. Some of these research results were granted the Nobel Prize. Thomas Hunt Morgan used Drosophila to demonstrate his hypothesis of chromosomal legacy and got the Nobel Prize in 1933 [9]. Hermann Joseph Muller described several principles of genetics, such as the effects of X-rays on mutation rates, for which he won the Nobel Prize [10]. In 1955, Edward B. Lewis, Christiane Nüsslein-Volhard, and Eric F. Wieschaus exploited Drosophila to demonstrate how genes control embryonic development [11]. In 2004, Richard Axel explained the working mechanism of olfactory receptors and the olfactory system with Drosophila experiments [12]. Hoffmann and Bruno Lemaitre discovered the function of the Toll gene and Toll-Mediated Innate Immunity in Drosophila [13]. Mammalian homologs of Toll receptors were discovered by Beutler. Toll-like receptors explain how septic shock can be triggered by bacterial debris with triggering the immune response. As can be understood, many studies have been completed with Drosophila. As a model organism Drosophila is also used in developmental biology studies. For instance, Drosophila is used in studies related to many developmental processes such as neuron development and embryonic development [14, 15]. In mammals, symmetrical division of the precursor stem cells into the intermediate cells called "secondary precursors" is the first critical stage of neuronal development. Until recently, it was not known whether mammals and fruit flies share common features in neuronal development. Bello et al. has shown that there are intermediary precursors in the Drosophila brain. Ceron et al. proved that these divisions also depend on the stage of the development [16, 17]. In the first larva, the neuroblasts partition evenly to shape two separate neuroblasts, while in later phases of brain development, most of the neuroblasts divide asymmetrically. These findings have been shown that some of the key points of neuronal proliferation can overlap in mammals and insects.

### *Caenorhabditis Elegans*

*Caenorhabditis elegans* is a microscopic, non-pathogenic organism. They are free-living soil nematodes, approximately 2 mm tall, 65 µm thick [18]. In laboratory conditions, they can easily survive by feeding on bacteria (*Escherichia coli* OP50 strain) on an agar substrate in a petri dish [19]. Also, as a stock, they can be frozen at -80°C or in the vapor of liquid nitrogen and stored indefinitely. C. elegans is also suitable for performing sophisticated genetic techniques such as genome editing, and transgenesis by microinjection [20, 21]. Transparent body of C.elegans provides great advantages during the tracking of the expression of various fluorescent-labeled proteins, including green fluorescent protein, in living animals. Because their body is transparent and their development is stereotypical, every cell in the generation can be traced back to the egg [22, 23]. Therefore, the fate of each cell from the zygote to the adult is well known. Between 1970 and 1980, the cell line of this nematode from fertilized egg to adult was characterized by laser ablation microscopy.

Since they have a short life span, they are frequently used in studies related to aging and lifespan. In addition to gene expression studies using a green fluorescent protein because they have a transparent structure [24]. More than 50 genes that control aging have been identified in *C.elegans* so far, and most of these genes are homologs of genes in other living organisms. *C. elegans* has around 20,000 genes and 6 chromosomes in total. It has been determined that a significant portion of these genes resemble human genes to a great extent. Therefore, *C. elegans* is an important model organism for

the discovery and functional characterization of eukaryotic genes. The *C. elegans* genome is the first multicellular, second eukaryotic organism to be sequenced. The determination of the genome sequence makes it easy to identify many diseases and examine the effects of various chemicals. In addition, techniques such as RNAi technology and transgenic generation are readily applicable. Although it is a non-mammalian system, it is used as a model organism in many human diseases such as metabolic syndrome, aging, cancer, neurodegenerative diseases, depression, and neural degeneration. It includes muscle cells, the nervous system, epidermis, intestine, gonad, glands, and defecation system [25, 26].

Sydney Brenner, Robert Horvitz and John Sulston were awarded the 2002 Nobel Prize in Physiology or Medicine at C.elegans for organ realization and relating to the programmed future. In 2006, the Nobel Prize in Physiology or Medicine was awarded to Andrew Fire and Craig Mello for their discovery of RNA interference in C.elegans [27].

### *Saccharomyces Cerevisiae*

*S. cerevisiae* (budding yeast) is a model organism that is an analog of the *E.coli* model organism in prokaryotes and eukaryotes [28]. Yeast is the first eukaryote whose genome has been fully sequenced. *S. cerevisiae* is one of the most widely used eukaryotic models not only for cellular mechanisms such as regulation of gene expression, signal transduction, the cell cycle, metabolism, apoptosis, but also aging, neurodegenerative diseases, and many other models of biological processes. 30% of the genes involved in human diseases can have orthologues in the yeast proteome [29-31]. Yeast culture is extremely simple, economical, and fast. In nutrient-rich media, cells double in about 90 minutes. Because they are interrupted by budding, interpretation of the cell cycle can be made by looking at bud size, and the cell cycle can be blocked at various levels. S.cerevisiae yeasts can be found in haploid or diploid state. When normal conditions, diploid cells reproduce by mitosis, but under extreme conditions such as carbon or nitrogen starvation, they form spores by meiosis.

Spores are found in structures called ascus (four haploid cells in a thick cell wall). Haploid S.cerevisiae cells have about 15 megabases of DNA and 16 linear chromosomes [32]. The sizes of these chromosomes are between 200-2200 kb and the largest yeast genome is about 100 times smaller than a normal mammalian genome [33]. There are three structural elements in the yeast chromosome: replication centers (ARS elements), centromeres (CEN elements) and telomeres. In yeast chromosomes, artificial chromosomes that allow cloning of large DNA structures are more prominent than other cloning systems [34].

### *Xenopus Laevis*

*Xenopus laevis*, additionally called the African clawed frog, is an African aquatic frog located in Sub-Saharan Africa [35]. They are particularly adaptable and might live on and reproduce in a number of situations. *Xenopus laevis* reproduce externally by fertilizing eggs outside the female's body. In the laboratory, frogs can reproduce their offspring year-round through simple hormone injections [36].

Although humans and frogs are genetically far apart, they have more similar terrestrial inheritance and evolutionary processes than bony fish. The whole genome sequencing and careful annotation of the two species showed a surprisingly high degree of adaptability [37]. Even in the duplicate *X. laevis* genome, since the two sets of chromosomes do not overlap, there are fewer functional deletions in duplicate copies [38, 39]. There are polyploid species in the *Xenopus* genus, which has many 18 chromosomes (36 in X. laevis and other tetraploid species, 72 in *X. amieti* and other octoploid species, *X. ruwenzoriensis* and other ten 108 of the diploid species), and there are 20 diploid chromosomes in the genus *Xenopus*. Although this model is using vertebrate development studies, it is not suitable for genetic studies. This is because the *X. laevis* is tetraploid [40, 41].

Adult females can lay eggs 2-3 times a year, and each spawning season can get thousands of eggs from one female. They are used as model organisms because they produce large embryos that can develop outside the mother's body. Eggs are surrounded by a gel coat and is about 1.5 mm in size. Embryo development occurs in similar to mammals. Therefore X. laevis using the development of embryonic studies [42].

### *Mus Musculus*

Mice (*Mus musculus*) are one of the most widely used model organisms in human developmental research. The main reason for the preference of *Mus musculus* is the similarity of mice to human genetics and physiology; however, mice and humans evolved and adapted to different environmental conditions.*Today*, *Mus musculus* has been recognized as an excellent mammalian model for studying various signs and diseases. *Mus musculus* using as a model organism for lots of diseases related to metabolism, development, nervous system diseases, immunity, and other diseases [43, 44].

Genomic studies have shown that there is significant genetic homology between these two species. These studies and the development of methods to produce transgenic, knockout, and knockout mice provide more motivation and powerful tools for research in mice and greatly increase the use of mice as model organisms. The research on mice has greatly promoted researchers' understanding of human biology. Mus musculus domesticus are characterized by 40 acrocentric chromosomes (2n = 40). 75 percent of mouse genes have a 1: 1 orthologous relationship to human genes, and they are likely that they retain their ancestral functions in both species. The Mouse Genome Database (MGD) is a database of links and similarities between mice models and human phenotypes and diseases. MDG data are important for understanding and explaining the similarities and differences between human and mice biology. The data show that Mus musculus is an ideal living species as a model organism with its genetic similarity [45-47].

### *Zebrafish (Danio rerio)*

*Zebrafish (Danio rerio)* is a tropical freshwater fish. After it was first used in research in the 1980s, it has become one of the most popular model organisms with the advantage of its widespread use. Zebrafish has become a very attractive model for biomedical studies due to its high reproduction rate, transparent embryos that develop ex-utero, and easy maintenance [48]. An average of 70% of human genes have at least one zebrafish ortholog. This similarity rate is higher than *Drosophila melanogaster*. Zebrafish have been used as model organisms since 1980. Since this date, many manipulative tools related to developmental processes (especially embryonic development) have been produced and developed. Because of the genomic similarity between zebrafish and humans, many of the developmental problems discovered in zebrafish are also seen in humans [49]. The development period of zebrafish embryos is very short. The zebrafish embryo is transparent, which allows scientists to easily follow the developmental process. Zebrafish complete all organ development 5 days after birth. Zebrafish can produce hundreds of offspring per week for this reason genetic mapping is possible [50, 51].

Table 1. Advantages and disadvantages of model organisms [54-56].

| Species | Advantages | Disadvantages |
|---|---|---|
| *Saccharomyces cerevisiae (yeast)* | • Destiny of each cell known<br>• Can use lots of different types of molecular techniques<br>• Genomic sequencing is complete.<br>• Can use cloning methods easily<br>• Cheap and easy to breed.<br>• Ease of maintenance | • No unique tissues<br>• It does not have physiology similar to human physiology. |
| *Caenorhabditis elegans (nematode)* | • Destiny of each cell known<br>• Can use lots of different types of molecular techniques<br>• Genomic sequencing is complete.<br>• Perfect genetics Hermaphrodites, self-insemination<br>• Ease of establishing the system<br>• Can use cloning methods easily.<br>• SNP mapping can be used.<br>• Cell cycle control similar to animals<br>• Cheap and easy to breed.<br>• Ease of maintenance | • Less similar to human than *Drosophila melanogaster*<br>• It does not have physiology similar to human physiology.<br>• Some embryological manipulations hard |
| *Drosophila melanogaster (fruit fly)* | • Destiny of each cell known<br>• Can use lots of different types of molecular techniques<br>• Genomic sequencing is complete.<br>• Ease of establishing the system<br>• Targeted gene corruption<br>• RNAi effective.<br>• Can use cloning methods easily.<br>• SNP mapping can be used.<br>• Transgenic animals easily produced<br>• Cheap and easy to breed. | • It does not have physiology similar to human physiology.<br>• Embryological manipulations hard |
| *Danio rerio (zebrafish)* | • Transparent embryo, because of this advantage, the embryonic developmental process can be observed more easily.<br>• The simplest vertebrate with the appropriate human genome<br>• Feasible embryological manipulation and large screening<br>• Organ systems similar to other vertebrates | • It does not have physiology similar to human physiology but *Danio rerio* is more similar to human physiology than *Saccharomyces cerevisiae, Caenorhabditis elegans,* and *Drosophila melanogaster*.<br>• Targeted gene modification difficult |
| *Xenopus laevis (frog)* | • Ectopic gene expression is possible in early vertebrate embryos.<br>• Excellent empirical embryology grafting induction preparations.<br>• Possibility of RNA injection into the identifiable blastomere.<br>• It has a transparent embryo and is large, so it is easy to manipulate. | • It does not have physiology similar to human physiology but *Danio rerio* is more similar to human physiology than *Saccharomyces cerevisiae, Caenorhabditis elegans,* and *Drosophila melanogaster*.<br>• Transgenic animal creation is difficult. |
| *Mus musculus (mouse)* | • It has a pathology similar to humans.<br>• Their developmental processes are similar to those of other mammals.<br>• Excellent tools for phenotypic characterization<br>• Targeted gene modification is easy<br>• Fully annotated genome | • Genetic manipulation is more difficult and complex than other model organisms.<br>• Maintain is expensive |

The *zebrafish* genome consists of 25 haploid chromosomes and 26,206 protein-coding genes. The orthologs of 70% of the genes that cause disease in humans are found in *zebrafish*. It shows a high similarity to mammalian organisms in terms of cellular structure and function. As a result of mutations created using mutagenic agents and genome editing tools, there are currently over 4000 transgenic and mutant *zebrafish* lines. In the systematic classification, disadvantageous genome duplications are observed in *zebrafish*, like other fish species in the Teleostei subclass to which they belong. This problem can be avoided by investigating the expression of these genes with more than one copy. Due to the lack of certain elements specific to the breast tissue, lung, prostate, and skin found in mammals, it cannot be used in modeling the diseases associated with these structures; however, it is a preferred model for investigating many different diseases such as muscle diseases, immunological diseases, infectious diseases, metabolic diseases. In addition, it is a suitable model organism for many different studies such as toxicity, drug screening, and behavioral anomaly studies [49, 52, 53].

## Organoids

Stem cells are the main cells that make up all tissues and organs of the human body. These undifferentiated cells are infinitely able to divide, self-renew, transform into organs and tissues, allowing them to create and protect tissues in the developing embryo and maintain tissue homeostasis in adults. An organoid is a mini-organ prepared in vitro in a three-dimensional (3D) culture medium and organoids are produced using stem cells. An organoid is simply defined as the structure that can regenerate, self-organize and mimic the structure and functions of the organ obtained from primary tissue or pluripotent cells under 3D conditions. Organoid cultures are 3D culture systems, were invented in 2009 by Sato et al. Stem cell technologies show promise in modeling developmental processes, analyzing disease mechanisms, understanding related mechanisms, and developing potential treatments [57-60].

Organoids derived from human IPCs have so far been established for the gut, kidney, brain, and retina, among others [61]. Most of the organs studied have proven to be self-organizing in rearrangement experiments from embryonic tissues, indicating that organoids can be produced if organogens are in principle derived from IPCDs. Conventional 2D cell culture relies on adhering to a flat surface, typically a glass or polystyrene petri dish, to provide mechanical support to the cells. Cell growth in 2D layers allows access to similar amounts of nutrients and growth factors contained in the medium, resulting in homogeneous growth and proliferation. In contrast to this situation, 3D cell culture is a model system. This model system enables cell aggregates to be formed in a tissue scaffold or liquid-based methods where structural proteins and other biological molecules. This structural proteins and other biological molecules found in living tissues as tissue spheroids or embedded cells mimic ECM. The most common way of 3D structure of organoids is through the use of solid extracellular matrix proteins that support cell growth and to which cells can adhere. Matrices are often used as a 3D culture medium that mimics the naturally provided scaffold support of tissue, The Engelbreth Holm-Swarm (EHS) matrix, a reconstructed basement membrane collected from mouse sarcoma and known by the trade names Matrigel, Geltrex, and Cultrex BME, has been crucial in the development of the organoid area [62-64].

Animal models are important for basic and applied research, but are time-consuming and often low in anatomical, physiological, and genetic similarity, which would be difficult to relate to human biology and pathology. Advances in cell biology, biomaterial design, and imaging technology have led to the investigation of increasingly complex biological questions. Therefore, physiologically in vitro tissue models are necessary to study human biology and developmental processes. Organoid technology is used as a model in many developmental studies. For instance, in an article published in 2020, the use of kidney organoids in regenerative medicine was referenced. In this article, it was referenced that congenital kidney anomalies were modeled on organoids and the complex cellular arrangements during kidney morphogenesis were clarified. In an article published by Niloofar et al. In 2020, it was stated that many studies were conducted on kidney development, physiology and diseases of organoids [65]. In 2017, Lullo et al. Using brain organoids, the molecular basis of nerve development and diseases associated with nerve development has been investigated [66].

When look at the advantages and disadvantages of organoids, he can be said that the benefits can be studied by modeling the relevant organ / disease rather than studying a complex system. Other advantages are that the consequences of the investigation are superior to the model organisms since the orgainds are created utilizing human stem cells. Contrasted with model organisms, probably the greatest benefit is that any living thing isn't harmed previously or after the study. When view the disadvantages, it is more difficult to manufacture than the alternatives. It is more expensive compared to other alternatives. The last and most significant disadvantage is the lack of inter-organizational communication in organoid systems. Human organoid systems basically mimic a part of the human body, not the whole body. As a result of this situation, it is not possible at this stage to test the interactions seen as a result of the complex structure of the human body with organoid systems [67-68]

## Computer (In silico) Modelling

Mathematical modeling and computer modeling research have a long history in developmental biology, but they have become more and more popular in recent years [69-70]. For instance, Ranjeet J. graduated from systems engineering in 1975. He then studied on 'A systems

approach to renal dialysis'. After that Lawrence at al. discovered a computer model of the kidney at 1992 [71]. Mathematical, computational and physical techniques have been carried out in biological and medicine to study phenomena at a wide range of scales, from the worldwide human population all of the manner down to the extent of individual atoms inside a biomolecule. In silico modeling method is to mimic living organism in computer environment. In computer modeling, the results are given predictively. It is a modeling based on algorithms and machine learning. Nowadays, machine learning (ML) has become very popular and is expected to grow exponentially in the coming years [72].

Science is basically about the how the interaction between ideas and reality. Recently, researcher's capacity to investigate both sides of the situation was limited. Technology has kept on growing cumulatively throughout the long years. As a result, real life predictions in biological and medical sciences have become more accurate. Biological sciences and medicine are generating more and more data. RNA sequences or genomes, and researcher rely heavily on computational methods to analyze and interpret them. In addition, computer models and simulations form the core of modern biology The need for data modeling and analysis to answer unsolved problems in the life sciences are driving the development of computer science and leading to real cross-fertilization "Biology and computer science or medicine and computer science". This has been made possible by machine learning. Machine learning is a branch of computer science that makes decisions using past experiences when it comes to making decisions for the future. It allows a model to learn automatically from experience based on data, without having to model it just like statistical models. ML creates an unknown rule from the given examples. Computer modeling has many different forms and types. Machine learning makes inferences from data with the help of algorithms. These algorithms can make inferences about the current situation as well as make predictions for the future. Due to these abilities, machine learning has a widespread use in cancer and other hereditary diseases diagnosis [69-73].

A computational model can run thousands of simulations. By running these simulations, scientists can identify the few laboratuary experiments needed to solve the problem. This has several benefits, including a significant reduction in research costs associated with biological studies and a reduction in the use of animal models, which is a controversial ethical issue. On the other hand, it also has some disadvantages. An appropriate algorithm should be chosen so that computer models give results similar to those in real life. Machine learning algorithms use a variety of statistical, probability and optimization techniques to learn from previous experience and detect useful patterns from large, unstructured and complex datasets. Algorithm selection is very important in the in silico model organism to be created [74-76].

## Conclusion

Subsequently, when we compare model organisms, organoids and in silico models, the creation of model organisms are simple and the expense are lower than the other options. Since the research will be conducted in a living organism, similarity of this method with real world results is higher than its alternatives. Inconvenience of model organisms are that we are currently working with animals with a limit of 70% genomic likeness. In the event that we take a gander at the benefit of organoids, organoids are a system obtained by human stem cells. In contrast to the model organisms, the problem of genomic similarity is not experienced in this system. Because of this feature, the rate of mimicking is high. If we talk about the disadvantages, it is hard to produce and it is a costly technique contrasted with its other options. Finally, if we look at in silico modeling, when the appropriate algorithm is selected and integrated, it will be easy to use in future research. It is easier to apply compared to organoids. The disadvantages are that the standard deviation rate may vary according to the algorithm created, so the standardization process is important in the in silico method. Its cost is high.

## Conflict of interest

There is not a conflict of interest.

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