

A Comprehensive Classification of Experimental Models Used in Epilepsy Research

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Introduction

Epilepsy is a chronic neurological disorder characterized by spontaneous, recurrent seizures, affecting over 50 million individuals worldwide. Despite its prevalence and impact on quality of life, the underlying mechanisms of epileptogenesis, seizure propagation, and drug resistance remain incompletely understood. Experimental models have thus become indispensable tools in epilepsy research, offering controlled environments to dissect the complex pathophysiology, evaluate new therapeutic agents, and develop innovative interventions such as gene therapy or cell transplantation. A well-structured classification of these models is critical for guiding researchers in selecting appropriate platforms that align with specific investigative goals whether they pertain to molecular mechanisms, electrophysiological patterns, behavioural phenotyping, or drug screening. This paper provides a detailed overview of the diverse experimental models currently used in epilepsy research, their classification schemes, applications, limitations, and how they are shaping the future of anti-epileptic drug discovery and mechanistic understanding. Within each category, models vary based on their etiology (e.g., acquired vs. genetic), seizure type (generalized vs. focal), duration (acute vs. chronic), and their translational relevance to human epilepsy syndromes. The refinement and classification of these models not only enhance reproducibility and interpretation of experimental data but also facilitate regulatory approval processes and bridge the gap between preclinical and clinical research [1].

Description

Experimental models of epilepsy are indispensable for mimicking various aspects of human epileptic syndromes, allowing researchers to explore seizure generation, epileptogenesis, treatment efficacy, and long-term comorbidities. Broadly, these models are classified into *in vivo*, *in vitro*, and *in silico* models, each with subcategories tailored to specific research questions. *In vivo* models the most extensively used are based on whole-animal systems such as rodents, zebra fish, or non-human primates. These models can be further classified into chemically-induced, electrically-induced, genetic, and lesion-based models. Chemically-induced models, including those using kainic acid, pilocarpine, Pentylentetrazole (PTZ), or bicuculline, are widely utilized for inducing acute or chronic seizures that mimic temporal lobe epilepsy or generalized seizures. The kainic acid and pilocarpine models, for example, closely replicate status epilepticus followed by spontaneous recurrent seizures, making them suitable for studying epileptogenesis and testing anti-epileptogenic drugs. Electrically-induced models, such as kindling and electroshock models help examine progressive changes in brain excitability and are particularly useful in modeling chronic epilepsy [2].

In vitro models, on the other hand, include brain slices, organotypic cultures, and dissociated neuronal cultures, allowing direct visualization and manipulation of neuronal activity at the cellular or synaptic level. These models

are ideal for studying the microcircuitry underlying epileptiform discharges and testing pharmacological agents at high precision. They offer advantages in terms of accessibility, experimental control, and reduced animal use but may lack the systemic complexity of an intact organism. Moreover, the rise of human stem cell-derived brain or ganoids and iPSC-based models has opened new frontiers in personalized epilepsy research, especially for rare genetic epilepsies. *In silico* models, which use computational simulations of neuronal networks, ion channel behaviour, or large-scale brain dynamics, complement biological models by offering scalability, mechanistic hypothesis testing, and the ability to simulate long-term effects or multiple parameters simultaneously. These models are increasingly used in conjunction with machine learning algorithms for seizure prediction and drug discovery [3].

Despite their utility, each model has inherent limitations. Animal models, while biologically rich, may not always fully replicate human epilepsy in terms of seizure phenotype, ethology, or treatment response. Species differences in pharmacodynamics and brain organization can lead to discrepancies in translational outcomes. Furthermore, the induction of epilepsy in animals may rely on methods (e.g., high-dose chemical convulsants) that do not naturally occur in human patients. *In vitro* models, while highly controlled, cannot mimic systemic immune responses, behavior, or long-term plasticity, while *in silico* models depend heavily on the accuracy of the underlying biological data and assumptions. Therefore, the choice of model must be made thoughtfully, often using combinatorial approaches that incorporate multiple platforms for a holistic understanding. Recent trends in epilepsy modelling emphasize multimodal integration, where *in vivo* electrophysiology is combined with imaging, genomics, and behavioural analysis, or *in vitro* findings are validated in animal models. The classification of epilepsy models continues to evolve, incorporating new technologies such as optogenetics, CRISPR-based gene editing, and wearable EEG systems that enhance data richness and translational relevance [4].

The future of epilepsy modelling lies in integrative, multimodal approaches that combine the physiological relevance of animal models, the precision of cellular systems, and the predictive power of computational tools. Moreover, the integration of human-specific models such as iPSC-derived organoids and the application of AI-driven analysis promise to close the gap between laboratory research and patient care. As the field continues to evolve, the refinement of classification systems for epilepsy models will remain essential for enhancing research rigor, reproducibility, and translational impact. Ultimately, the continued advancement of experimental models will be vital in the global effort to better understand, prevent, and treat the wide-ranging and often devastating effects of epilepsy. Over the decades, a wide spectrum of experimental epilepsy models has emerged, ranging from acute chemically-induced seizures to chronic models of temporal lobe epilepsy, from *in vitro* neural cultures to sophisticated transgenic and optogenetic animal systems. These models can be broadly classified into three principal categories: *in vivo* (whole-animal) models, *in vitro* (cellular and tissue-based) models, and computational (*in silico*) simulation [5].

Conclusion

Experimental models remain the cornerstone of epilepsy research, providing the necessary platforms to investigate disease mechanisms, screen therapeutics, and ultimately translate scientific discoveries into clinical interventions. As this review illustrates, the classification of epilepsy models spanning *in vivo*, *in vitro*, and *in silico* domains enables researchers to strategically select the most appropriate tools for specific research objectives,

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whether investigating genetic mutations, neural circuit dysfunction, or drug efficacy. In vivo models, especially those induced chemically or genetically, have contributed significantly to our understanding of seizure dynamics and treatment responses. In vitro systems allow for fine-tuned cellular and molecular experimentation, while computational models offer the ability to test theoretical frameworks and simulate complex systems without ethical concerns. Each model class, while powerful, has its strengths and limitations, and no single model can encompass the full spectrum of human epileptic conditions.

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Conflict of Interest

There are no conflicts of interest by author.

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