Virtual Cells as Modeling Tools for Epigenetics, Ploidy, and Cell Fate under Quantum Principles

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Resumo

A variação de ploidia tem se mostrado um mecanismo fundamental de adaptação celular em organismos como fungos e células tumorais humanas, promovendo flexibilidade epigenética e diversidade de destinos celulares. Paralelamente, os avanços em modelagem computacional e inteligência artificial (IA) têm permitido a construção de células virtuais (AI Virtual Cells – AIVCs) capazes de simular comportamentos celulares complexos em contextos tridimensionais e multi-escala. Este trabalho propõe uma revisão integrativa e um modelo conceitual que conectam a variação de ploidia, a instabilidade epigenética e a teoria quântica da mutação adaptativa ao desenvolvimento de AIVCs. A partir da análise de casos biológicos e modelos matemáticos, discutimos como a simulação de flutuações torsionais do DNA e transições epigenéticas pode informar a construção de "gêmeos digitais" celulares capazes de prever destinos celulares sob diferentes pressões seletivas. Defendemos que a próxima geração de AIVCs deverá integrar algoritmos de aprendizado profundo, princípios de mecânica estatística e simulações quânticas para captar a plasticidade genômica e epigenética que emerge de estados de ploidia variável. A proposta amplia o escopo das modelagens existentes, com implicações para biologia do câncer, diferenciação celular, biologia da regeneração e medicina personalizada.

Palavras chaves: células virtuais, epigenética, quântica, modelagem, destino celular.

Abstract

Ploidy variation has emerged as a fundamental mechanism of cellular adaptation in organisms such as fungi and human tumor cells, promoting epigenetic flexibility and diversity of cell fates. In parallel, advances in computational modeling and artificial intelligence (AI) have enabled the development of virtual cells (AI Virtual Cells – AIVCs) capable of simulating complex cellular behaviors in three-dimensional, multi-scale contexts. This work proposes an integrative review and a conceptual model that connect ploidy variation, epigenetic instability, and the quantum theory of adaptive mutation to the development of AIVCs. Based on the analysis of biological case studies and mathematical models, we discuss how the simulation of DNA torsional fluctuations and epigenetic transitions can inform the construction of cellular "digital twins" capable of predicting cell fate under different selective pressures. We argue that the next generation of AIVCs should integrate deep learning algorithms, principles of statistical mechanics, and quantum simulations to capture the genomic and epigenetic plasticity emerging from variable ploidy states. This proposal broadens the scope of existing models, with implications for cancer biology, cell differentiation, regenerative biology, and personalized medicine.

Keywords: virtual cells, epigenetics, quantum, modeling, cell fate..

1. Introduction

Ploidy variation (the number of chromosome copies present in a cell) emerges as a fundamental morphological mechanism of adaptation in various organisms - from fungi to tumor cells - shaping regulatory networks and creating new cell fates [1,2]. From this perspective, virtual cells (also referred to as AI Virtual Cells – AIVCs) arise as computational models capable of integrating multi-omic and morphological data to simulate, predict, and reprogram cellular behaviors in diverse contexts, including those influenced by multiple regulatory networks [3,4,5].

Historically, the concept of the virtual cell originated in the early 2000s with the development of The Virtual Cell software [3], which enabled the simulation of biochemical networks in 2D. In subsequent decades, the platform evolved to encompass 3D modeling and multi-omic integration, giving rise to Virtual Cell-Based Assays (VCBAs) applicable to toxicological and pharmacokinetic prediction [6,7]. Graepel et al. [4] reviewed the state of the art in VCBAs, emphasizing the importance of incorporating reaction databases and kinetic parameters to enable extrapolation from in vitro to in vivo scenarios. Bednarczyk et al. [8] expanded this scope by extending VCBAs from 2D to 3D models, bringing them closer to

the actual architecture of tissues. Bunne et al. [9], in turn, examined the priorities and opportunities for building AI-based virtual cells, highlighting the need to integrate deep neural networks capable of learning directly from multi-omic experimental data.

Together with the advancement of artificial intelligence (AI), the development of virtual cells is expected to evolve toward "Multilevel Information" models. This means that to understand complex cellular processes—including cell fate and epigenetics—it is necessary to integrate computational layers ranging from physical-quantum modeling to graph neural networks (GNNs) and generative models [10]. Accordingly, the next generation of virtual cells, shaped by the unification of statistical mechanics methods and spatial modeling to simulate both molecular diffusion and 3D signal transduction, will need to combine cellular, quantum, omic, and molecular dimensions [5].

Given this context, the present article aims to develop a theoretical and computationally expandable conceptual model that integrates ploidy variation, epigenetic transitions, and principles of quantum mechanics into the development of AI-based virtual cells (AIVCs). The goal is to simulate cell fate decisions in complex biological systems. The rationale for this approach lies in the need to represent, in a multiscale and mechanistically informed manner, the dynamic processes governing cellular plasticity in contexts such as stress-driven adaptation and mechanisms like carcinogenesis, aging, and regeneration. This would make it possible to predict and manipulate dynamic cell states under different environmental and genetic pressures.

2. Methodology

This article is structured into two complementary axes. The first is an integrative review through the collection and critical analysis of literature on ploidy in fungi and cancer, quantum adaptive mutations, stochastic epigenetics, Petri networks, virtual cells (VCBA), and machine learning applied to biological systems. Sources were drawn from databases including PubMed, Scopus, Web of Science, BVS, and arXiv. A theoretical modeling proposal was developed to connect ploidy-induced cell states with epigenetic transitions and quantum states, along with multi-layered virtual cell components: (i) physical-quantum, (ii) epigenetic, (iii) genomic, and (iv) Petri network layers. Yeast models were employed to simulate scenarios of adaptation, differentiation, and drug response in relation to ploidy variation and epigenetic reprogramming.

3. Results

3.1. Ploidy in Fungi and “Virtual” States

In fungi such as *Saccharomyces cerevisiae*, *Candida albicans*, and *Cryptococcus neoformans*, ploidy variation (polyploidy, aneuploidy) occurs rapidly under environmental stress [11]. Temporary polyploidy (e.g., tetraploid states) and aneuploidy allow fungal populations to test multiple “cell fates” before returning—or not—to the more stable euploid state. For instance, in *Cryptococcus neoformans*, so-called “titan” cells can reach ploidy levels from 4n up to more than 64n, exhibiting thick cell walls and enlarged capsules—features typically associated with stress adaptation—indicating a transitional cellular state that resembles a fungal “virtual cell”: a state of multiple fate possibilities, induced by polyploidy and regulated by histone modifications and cell cycle checkpoints [11].

In *Candida albicans*, the transition from a tetraploid to a “quasi-diploid” state occurs through chronic chromosome loss during parasexual cycles, even in the absence of meiosis. This highlights a nonlinear cell fate trajectory driven by chromosomal instabilities and epigenetic remodeling. These intermediate states can be viewed as “virtual cells” capable of exploring new metabolic and morphological profiles before stabilizing into a fixed phenotype [11].

Chiarugi et al. [12] discuss how fungal systems can be formally modeled using process logic methods and Petri nets, anticipating the idea that fungi, due to their relatively simple genomes, serve as ideal “laboratories” for testing hypotheses about ploidy - epigenetic plasticity. Heydari et al. [13] demonstrated that virtual models can predict cellular responses to different substrate topographies, showing that changes in cell morphology - including ploidy-induced shifts in volume and shape - are coupled with epigenetic changes that guide cell fate.

3.2. Ploidy in Tumor Cells: Instability, Aneuploidy, and Adaptability

In a connection between humans and fungi, human tumor cells also exhibit ploidy alterations that precede aneuploidy and the development of malignant subclones. Subsequent ploidy reduction - through multipolar mitoses and defective chromosomal reintegration - generates strong genomic instability [1], providing fertile ground for the emergence of adaptive subpopulations with selective advantages. According to Shyh-Chang & Luo [14], these ploidy transitions can be modeled as quantum jumps between different DNA torsional states, where slow variables (torsional angles) act as order parameters, determining when and how chromatin shifts conformation - directly impacting gene expression and cell fate.

In this context, relationships between specific aneuploidies and epigenetic remodeling help explain how aneuploid subclones explore new metabolic and immune niches [1,2]. These studies are complemented by models from Rabajante et al. [15], who use stochastic equations to capture the impact of epigenetic modifications (including point mutations and epimutations) on stem cell fate.

Furthermore, Yang et al. [16] address the development of AI-based virtual cells for cancer research, emphasizing that variable ploidy states in tumors must be integrated into deep neural networks capable of capturing gene expression patterns and epigenetic reorganizations in tumor subpopulations. These models allow simulation of drug responses, prediction of resistance mechanisms, and identification of vulnerabilities associated with increased ploidy - especially relevant for drugs targeting cell cycle checkpoints or homologous recombination regulators.

3.3. Quantum Models for Cell Fate Decisions

The proposal that cell fate decisions may, in part, reflect quantum processes has gained traction in recent decades. McFadden & Al-Khalili [17] suggested that adaptive mutations could be explained by accelerated quantum decoherence, favoring certain mutant states under environmental pressure - a concept known as the “quantum adaptive mutation model.” For

example, in an engineered system based on immortalized mouse embryonic fibroblasts (MEFs), expression of the SV40 large T antigen (TAg), essential for clonal growth, depends on the correction of a previously introduced mutation in the polyadenylation (polyA) site of the gene [18].

In this context, functional restoration of the mutated site is interpreted as a directed adaptive mutation event, mediated by base tautomerism and quantum coherence, in which genotypic states coexist in superposition until the selective environment - such as doxycycline presence and CRE-lox activation - induces wavefunction collapse to the functional mutation [18]. This base-dependent selection hypothesis aligns with the proposal by Torday and Miller Jr. [19], who view the unicellular zygote as a quantum agency responsible for filtering and reconfiguring inherited epigenetic marks and establishing the trajectory of multicellular development based on molecular superposition states and epigenetic reprogramming.

Moreover, as demonstrated by Scott et al. [20], tetraploid yeast strains grown under suboptimal carbon sources display a significantly broader range of adaptive mutations than haploid or diploid strains, expanding the accessible genotypic and epigenetic landscape. This expansion, associated with gene redundancy, allows beneficial mutations to arise without immediate deleterious effects, while unstable epigenetic states are buffered, facilitating trajectories of adaptation and differentiation. In this context, cell fate emerges as the dynamic interaction between chromosomal copy number, epigenetic markings, and the influence of quantum fluctuations in DNA torsional angles.

Building on theoretical studies, computational approaches ranging from early models by Loew and Schaff [3] to advances by Graepel et al. [4] and Johnson et al. [5], highlight the potential of virtual cells to simulate gene regulatory networks, ploidy variation, metabolic signals, and quantum coherence in real time. Modeling DNA torsional states according to the adiabatic Schrödinger equations proposed by Shyh-Chang and Luo [14] enables simulation of transitions between energy minima corresponding to the active and inactive forms of the polyA site. When coupled with Langevin–Fokker–Planck equations to map epigenetic fluctuations - as used by Rabajante et al. [15] - these computational tools allow prediction of cell fates under varying selective pressures, further refined through machine learning algorithms that capture nonlinear interactions among ploidy, metabolism, and genomic instability.

In agreement, Guo et al. [21] contribute to this framework by describing how transgenerational adaptations in organisms exposed to controlled conditions - such as fungi, plants, and animals - emerge from interactions between genetic mutations, epigenetic alterations, and structural instability. In Volvariella volvacea, for instance, successive subcultures induce oxidative stress, compromise mitochondrial and nuclear integrity, and lead to senescent states associated with epigenetic changes and functional loss. In zebrafish and rats, heritable changes in methylation patterns of genes such as esr1 are observed across several generations following exposure to agents like cadmium, reinforcing the notion that cell fate is shaped by epigenetic inheritance under prolonged environmental influence. These processes are consistent with the role of quantum fluctuations and DNA torsional reorganizations, which can be simulated in computational models as transitions between superposed epigenetic states and their collapse into stable conformations [21].

The theoretical structure for this complexity is complemented by Djordjevic and Djordjevic [22], who model mutations, aging, and cellular evolution using quantum Markov chains with or without memory and Lindblad master equations, which describe decoherence induced by environmental factors. These models interpret adaptive mutations as jumps between genetic and epigenetic states favored by selective pressures, especially under stress, aligning with the principles of directed adaptive mutation proposed by Bordonaro et al. [18]. Moreover, they provide theoretical support for the use of virtual cells as simulators of open quantum biological channels, capable of representing how a cell population evolves under diverse environmental conditions.

In the diversity of environmental conditions, the epigenetic landscape reformulated by Greulich, Smith, and MacArthur [23] reinforces this adaptive paradigm by modeling cell fate as the navigation of a cell among epigenetic attractors shaped by molecular noise, chromatin remodeling, and metabolic instabilities - a scenario in which ploidy variation and quantum coherence act as modulators of trajectory. This view is expanded by Guo et al. [21], who observe that in both sexually reproducing organisms and clonally reproducing systems, the unicellular state acts as the initial builder of the epigenetic niche, defining methylation and acetylation configurations that guide future adaptive responses.

3.4. Virtual Cells and In Silico Modeling: Multi-Omic and Multiscale Integration

The construction of artificial intelligence-based virtual cells (AIVCs) represents a significant advancement in computational modeling of biological systems, offering dynamic three-dimensional environments - often referred to as “digital twins” - capable of reproducing complex cellular behaviors and exploring interactions at the molecular, cellular, and tissue levels [5]. Loew and Schaff [3] were pioneers in describing the Virtual Cell as an environment for cellular modeling through reaction–diffusion equations and mass balance calculations, laying the foundation for subsequent approaches. Building on this, Comenges et al. [6] expanded these foundations by reviewing the principles of the Virtual Cell Based Assay (VCBA), demonstrating how submodels of chemical fate, intracellular partitioning, cell growth, and toxic effects can be integrated to predict intra- and extracellular concentrations over time. Moreover, in describing the state of the art and future directions of the VCBA, its applicability was confirmed for high-throughput screening and its integration with physiologically based kinetic (PBK) models for in vitro–in vivo extrapolation. In practice, integrating VCBA with PBK modeling optimized predictions of systemic toxicity based on experimental data from HepG2 and HepaRG cell lines [4,24].

The leap to three-dimensional environments extended VCBA capabilities to simulate compound exposures in HepaRG spheroids segmented into concentric layers. This 3D model captured spatiotemporal variations in the diffusion of toxicants - such as acetaminophen - and enabled integration of omics, biophysical, and microscopy data with kinetic

parameters, enhancing predictive robustness and aligning with the 3Rs principles (replacement, reduction, and refinement of animal use) [8]. As a result, the redefinition of virtual cells as dynamic 3D “digital twins” unifies top-down (phenomenological) and bottom-up (molecular) models, emphasizing that, while reductionist cell biology has fragmented data across multiple scales, the standardization of inputs and outputs and the modular structuring of information are essential to enable interoperability across different modeling approaches and descriptive levels [5].

Regarding ploidy variation, changes in chromosomal copy number that result in genomic drift [15], selective advantages, or trigger pro-oncogenic instabilities [6], can be represented by “digital twins” (with modules that automatically recalculate the effect of ploidy on gene expression, nucleotide availability during replication, and the probability of chromosomal segregation errors) or by mathematical models of gene regulatory networks (demonstrating how epigenetic perturbations can induce transitions between deep valleys of the phenotypic landscape) [10]. Additionally, epigenetic regulation can also be modeled within “digital twins” through stochastic equations representing the competition among histone-modifying enzymes [25]. Alarcón et al. [25] showed that fluctuations in the availability of metabolic cofactors - such as S-adenosylmethionine (SAM) and acetyl-CoA - lead to epigenetic tipping points. In this context, AIVCs based on “quasipotential landscapes” can simulate epigenetic interventions that restore healthy attractor states and inhibit uncontrolled proliferation.

Furthermore, according to Ham et al. [26], cell fate decision systems mapped and reprogrammed by combining RNA trajectories, epigenomic profiles, and physical parameters may constitute “digital twins” that integrate multiple regulatory layers. Accordingly, genetic and epigenetic adaptations under controlled experimental conditions are essential for calibrating virtual cells that simulate responses to drugs or environmental stressors [16]. In toxicological/pharmacological simulations, AIVCs that integrate omics-based foundational models with interpretability layers make results more accessible and explainable, serving as predictors and references for cell transitions in events such as tumorigenesis and differentiation [9]. In this oncological dimension, AIVCs can reconstruct continuous flows of cell states in rare tumors, using Universal Representations at the tissue scale and individual clinical data to generate personalized digital models that predict treatment responses [11].

However, Bunne et al. [9] warn that building complete AIVCs requires overcoming obstacles such as the absence of standardized digital models and the lack of evaluation metrics, proposing collaborative benchmarking frameworks. At the same time, the AIVC concept, when proposed as a multiscale information model, will demand the combination of quantum computing and spatial AI so that future virtual cells can perform advanced quantum simulations to model subatomic molecular interactions and enhance predictions of cell fate, 3D stochastic simulations of biochemical reactions, and capture discrete and stochastic events in large molecular populations [10,27].

4. Discussion

4.1. Hypothesizing an Integrated, Multilevel, Multi-Omic Model for Future Mechanistic Elucidations

The emergence of integrated approaches to understanding cell fate highlights the need for models that coherently and reproducibly articulate distinct levels of biological organization - from quantum physics to adaptive population dynamics - applying a translational framework grounded in individual cellular phenotypic profiles [1,28,29,30]. In this context, we propose a theoretical framework that combines physico-chemical principles and mathematical models applicable to the simulation of cellular processes on digital platforms, using yeast as a model organism. The goal is to capture interactions among quantum behavior of nitrogenous bases, epigenetic regulation, ploidy variation, and cell differentiation decisions.

To this end, we hypothesize that tautomeric transitions induced by quantum tunneling in DNA bases can be modulated by local epigenetic signals and by the genomic context determined by ploidy. When occurring during replication, such events may generate targeted mutations that influence cell fate. We model this system as a network of multiscale stochastic transitions, based on Petri nets with continuous modulation by multi-omic variables.

Building on prior discussions, we treat quantum DNA tautomerism as a stochastic and reversible molecular trigger for spontaneous mutations, especially under conditions of cellular stress or metabolic dysregulation. This is coupled with the idea of controlled windows of informational instability, where the outcome may be the introduction of adaptive point mutations. The rate of transition of a base to its tautomer can be modeled using the WKB (Wentzel–Kramers–Brillouin) approximation for quantum tunneling:

$$K_t \propto \exp\left(-\frac{2}{\hbar}\int_{x''}^{x'} \sqrt{2m[V(x)-E]}\, dx\right) \quad (1)$$

Where:
K_t: tautomerization rate
x’,x”: potential barrier limits between the keto and enol (or amino–imino) forms
m: proton mass
V(x): potential energy profile of the hydrogen bond in the nitrogenous base
E: ground state energy
$\hbar$: reduced Planck constant

If a base is in a tautomerized state at the moment of replication, the likelihood of incorrect pairing increases. This is represented by the probability:

$$P_{mut} = f_t \cdot P_{mis} \quad (2)$$

Where:
$f_t = \frac{(1)}{(1)+k_b}$: fraction of bases in the tautomerized state (with kb being the rate of return to the normal state)
Pmis: probability of mispairing given the tautomeric form

Consequently, the influence of epigenetics (E) and ploidy (ρ) can be introduced as modulators of replication fidelity and mutation fixation, represented by the following formula:

$$M = \alpha \times \frac{E}{(1+\beta\, e^{(-\gamma\rho)})} \quad (3)$$

Where:
M: modulation factor of the mutation fixation rate
E: epigenetic state
ρ: relative ploidy (e.g., 1 = diploid, 2 = duplicated, etc.)
E_0: chromatin opening threshold
α, β, γ: fitting constants

As a final result, the adaptive mutation rate (μ_{adapt}) generated by quantum tautomerism can be expressed as:

$$\mu_{adapt} = P_{mut} \cdot M \quad (4)$$

Furthermore, μ_{adapt} can also be represented through a Petri Net structure as:

$$\mu_{adapt} = c \cdot P(P2) \cdot P(P3) \cdot P(P4) \cdot f(\rho) \quad (5)$$

Where:
c: kinetic constant for mutation fixation
P(Pi): probability that place Pi is marked (occupied) - reflecting epigenetic states, stress, and tautomerism
f(ρ): ploidy sensitivity function, for example:

$$f(\rho) = 1 + \alpha(\rho - 1) \quad (6)$$

With:
ρ: ploidy level (1: haploid, 2: diploid, etc.)
α: adjustable parameter expressing how much ploidy affects mutation probability (positive for facilitation, negative for inhibition)

Thus, based on the connections between equations (1) to (6), which are useful for determining the final adaptive mutation rate in conjunction with Petri Net modeling - a mathematical framework composed of places (states), transitions (events), and tokens (state markers) - one can define places (e.g., stable DNA, environmental stress, formation of tautomeric base pairs, epigenetic changes, and alterations in genomic copy number) and transitions (e.g., quantum tautomerism induction, mutation occurrence, fixation, and cell fate modulation). By integrating these levels, the network enables simulation of how quantum mechanical interactions (e.g., proton exchange in nitrogenous bases), parameterized by experimental data, contribute to cell fate decisions.

As such, future simulations may benefit from digital yeast models due to their ploidy plasticity, relatively simple epigenetics, and genomic traceability. This can be achieved through virtual cells calibrated with real omics data from strains exposed to stress conditions.

In this way, a first step is taken toward a theoretical and computational platform capable of unifying different layers of cellular regulation - from quantum physics to systems biology - into an integrated, explainable, and iterative architecture. Translating this approach to complex organisms will depend on the scalability of regulatory layers, but the use of yeast allows validation of universal principles applicable to understanding cell trajectories in cancer, development/aging, and regeneration.

5. Conclusion

The interconnection among chemistry, physics, and biology constitutes an emerging paradigm necessary to understand life as a system of phase transitions, noise, and epigenetic attractors within a dynamic landscape. In this context, understanding how cells can change their fate unifies current trends in quantum theory, molecular and cellular biology, biophysics, biochemistry, artificial intelligence, and mathematical modeling - converging on the concept of Artificially Intelligent Virtual Cells (AIVCs). These central actors of this review play a vital role in predicting and simulating various cellular outcomes in increasingly controllable in silico environments.

Immersed in this integration, variations in ploidy - whether temporary or permanent - may become an integrative link for cellular mechanisms through mechanistic elucidations enabled by AIVC-based modeling. Such variations emerge as key focal points for acting as multiplexers of genomic and epigenomic information, exploring multiple phenotypic possibilities before a final fate is stabilized.

In this regard, the theoretical and hypothetical multilayered framework presented in this work offers profound implications for understanding complex mechanisms such as the origin and evolution of cancer, cellular longevity, tissue regeneration, and even pharmacological responses. Moreover, it opens up the possibility of faithfully simulating these processes in silico, accelerating drug discovery, personalized therapies, and insights into the fundamental laws that govern life - that is, how energy, information, and matter interact to produce order in open systems, dissipative structures, and biological phase transitions.

Finally, it is worth emphasizing that the disciplined construction of AIVCs depends on continuous improvement of experimental models and validation through in vitro and in vivo studies. Therefore, the goal is not to replace traditional approaches but to complement them and build methodological and conceptual foundations for a new research agenda. This agenda envisions a computational ecosystem where physico-chemical, quantum, and multi-omics variables converge to reflect the core connections among physics, chemistry, biology, and mathematics.

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