Computational Modeling of Mitochondrial Network Disruption as a Dual-Use Phenomenon: A Defense-Oriented Framework for Risk Assessment, Resilience, and Early Warning

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Abstract: - The convergence of biology, artificial intelligence (AI), and automated digital systems is catalyzing a new class of research with inherent dual-use characteristics that can accelerate biomedical progress and support national security, while also risking the amplification of biological threats if misused [1], [2]. Mitochondrial networks, governed by non-linear dynamics, feedback loops, and near-critical phase behavior, constitute a particularly sensitive substrate in this context [4]–[7]. Consequently, computational modeling of mitochondrial networks should be conceptualized not merely as a tool for fundamental research, but as an element of modern biosecurity and cyberbiosecurity risk governance [3], [8].

This paper presents a computational model of mitochondrial network dynamics that is explicitly designed to be defense-oriented and dual-use-aware. The model is intentionally agnostic to specific biological agents: it uses an abstract stress input A(t) that does not represent a pathogen, toxin, chemical compound, dosage, or experimental protocol. Its purpose is not to optimize biological impact, but to identify instability thresholds, bifurcations, and early-warning indicators (e.g., the critical decline of mitochondrial membrane potential (ΔΨm) toward zero, increasing variance and oscillatory behavior in reactive oxygen species (ROS), and progressive mitochondrial network fragmentation) that can support resilience engineering and early warning. The framework aligns with contemporary dual-use AI governance by enabling the evaluation of "capability thresholds" for unacceptable risk without generating actionable knowledge of exploitation [2].

Overall, the study contributes a non-exploitative, systems-engineering-style tool for assessing mitochondrial resilience that can be used in biomedical and defensive settings (e.g., early warning, stress testing, safety evaluation) while remaining, by design, below dual-use capability thresholds.

Key-Words: - dual-use, cyberbiosecurity, mitochondrial network, non-linear dynamics, bifurcation, criticality, ΔΨm, ROS, resilience engineering, early warning

Received: March 17, 2026. Revised: April 19, 2026. Accepted: June 11, 2026. Published: July 9, 2026.

1 Introduction

Over the past decade, the life sciences have undergone a profound digital transformation: AI-assisted modeling, automated laboratories, high-performance simulation, and digital twins are increasingly used to analyze and optimize complex biological systems [2]. Parallel to this progress, policy and scientific communities warn that the same technologies may create dual-use concerns, i.e., analytical capabilities that, if misapplied, could lower barriers to misuse in biology [2].

This raises a pivotal research question: How can powerful biological models be developed without increasing the practical capabilities for harmful use?

We address this challenge through mitochondrial network dynamics. Mitochondria constitute a cell's critical "energy infrastructure" and exhibit non-linear behavior, feedback regulation via ROS, and sensitivity to perturbations [4]–[6]. These

characteristics make mitochondrial networks scientifically compelling while also raising dual-use considerations when models could be repurposed to map vulnerabilities. Our approach is explicitly defensive: the proposed framework intentionally excludes descriptions of specific agents, concentrations, protocols, or experimental scenarios. Instead, it analyzes general dynamic regimes and early-warning signals to support risk assessment and resilience.

In contemporary biosecurity thinking, biological resilience is increasingly treated as a component of critical infrastructure, particularly as biological research becomes cyber-physical (e.g., cloud platforms, automation, laboratory information systems) [3], [8]. Defense-oriented computational modeling can help identify risk thresholds and warning signals while avoiding operational details that could be exploited.

2 Theoretical Context and Dual-Use Framework

2.1 The mitochondrial network as a non-linear system

Mitochondrial function depends on a dynamic balance between fusion and fission that shapes morphology, mtDNA distribution, and the stability of membrane potential (ΔΨm) [4], [5]. These processes are coupled via non-linear feedback loops, including ROS-mediated regulation and stress responses [6]. The non-linear nature of these interactions implies that relatively small perturbations may yield disproportionate system-level effects, motivating a resilience-oriented modeling approach.

2.2 Criticality and phase transitions in mitochondrial networks

Network analyses indicate that mitochondrial networks may operate near a critical phase transition between fragmented and highly connected regimes [7]. Topological measures (e.g., the size of the most significant connected component, cluster-size distributions, percolation-like properties) exhibit finite-size scaling consistent with that of near-critical systems [7]. Proximity to criticality implies heightened sensitivity: small shifts in effective fusion/fission balance can trigger significant changes in network connectivity and functional stability. This provides a principled link between bifurcations/tipping points and the emerging literature on critical mitochondrial networks [7].

2.3 Cyberbiosecurity, dual-use, and national security relevance

Cyberbiosecurity is increasingly recognized as a strategic priority for protecting biomedical infrastructures, automated laboratories, and digital biological platforms [3], [8], [12]. In such settings, quantitative non-exploitative models are helpful: they can assess biological consequences of generic perturbations and test resilience without encoding operational attack details. This aligns with modern expectations that biological modeling at the AI–biology interface should incorporate safety-by-design constraints to avoid enabling misuse [2].

2.4 Energy Resistance Principle and a dual-use interpretation

Picard and Murugan's Energy Resistance Principle (ERP) frames living systems as energy-transforming circuits operating within an optimal zone between energy flux and resistance [9]. From a dual-use perspective, displacement outside this "Goldilocks zone" (by accident or intent) poses a systemic risk. We use ERP as an interpretive lens: our model can be viewed as mapping stability/risk regions and identifying early-warning signals that indicate departures from functional zones—without specifying how such departures could be experimentally induced [9].

2.5 Positioning relative to mitochondrial toxicity prediction models

AI/ML approaches are used to predict the mitochondrial toxicity of specific molecules using structural descriptors and supervised learning [10]. The present work is complementary: rather than predicting toxicity for particular compounds, it analyzes general dynamic regimes and instabilities that diverse stressors could induce. This design choice both broadens conceptual utility and reduces dual-use risk by avoiding molecule- or protocol-specific operational guidance.

3 Problem Formulation and Methods

3.1 Model variables and definitions

The framework uses coupled ordinary differential equations (ODEs) for network integrity and function:

- **M(t):** mitochondrial network connectivity/integrity
- **Ψ(t):** mitochondrial membrane potential (ΔΨm)
- **R(t):** reactive oxygen species (ROS)
- **μ(t):** fraction of mutant mitochondrial DNA

(heteroplasmy)
•**A(t):** abstract adversarial (stress) input

Dual-use safety note: A(t) does not represent a real agent, toxin, pathogen, chemical compound, concentration, or experimental intervention. It is an abstract stress variable used exclusively to stress-test system dynamics, identify instability thresholds, and detect early-warning regimes. The model provides no operational or actionable guidance.

3.2 Governing equations (numbered sequentially)

Eq. (1) Mitochondrial network dynamics:

$$(1)\ dM/dt = U(t)*M(t) - F(t)*M(t) - \alpha*R(t)*M(t)$$

where:
M(t) = mitochondrial network connectivity
U(t) = effective fusion rate
F(t) = effective fission rate
α = ROS-induced structural damage coefficient

Eq. (2) Membrane potential dynamics:

$$(2)\ d\Psi/dt = \beta*M(t) - \gamma*R(t)*\Psi(t) - \delta*A(t)$$

where:
Ψ(t) = mitochondrial membrane potential (ΔΨm)
β = stabilizing contribution of network connectivity
γ = ROS-induced membrane potential loss
δ = sensitivity to abstract stress input

Eq. (3) ROS dynamics (production increases as Ψ declines; clearance proportional to R):

$$(3)\ dR/dt = \eta*(1/\Psi(t)) - \lambda*R(t)$$

Simulation note: during numerical integration, we regularize the term 1/Ψ(t) by using Ψ_eff = max(Ψ(t), ε) with ε = 10^-2 (equivalently, η/(Ψ+ε)) to prevent numerical instability as Ψ→0 and to improve reproducibility.
where:
R(t) = reactive oxygen species (ROS)
η = ROS generation due to electron leakage at low ΔΨm
λ = antioxidant clearance rate

Eq. (4) Heteroplasmy dynamics (fission promotes segregation/expansion; fusion promotes complementation/dilution):

$$(4)\ d\mu/dt = s*F(t)*(1 - \mu(t)) - d*U(t)*\mu(t)$$

where:
μ(t) = fraction of mutant mtDNA (heteroplasmy)
s = selection/segregation coefficient during fission
d = dilution/complementation coefficient during fusion

Eq. (5) & (6) State-dependent fusion and fission rates:

$$(5)\ U(t) = U0*\Psi(t) / (\Psi(t) + ku)$$
$$(6)\ F(t) = F0*R(t) / (R(t) + kf)$$

where:
U0, F0 = maximal fusion and fission rates
ku, kf = half-saturation constants

Eq. (7) Abstract adversarial/stress input (dual-use-aware by construction):

$$(7)\ A(t) = a1*R(t) + a2*F(t) + a3*\mu(t)$$

3.3 Early-warning and risk index

Eq. (8) We define a composite risk index to monitor proximity to instability:

$$(8)\ D(t) = w1*R(t) + w2*\mu(t) - w3*\Psi(t) - w4*M(t)$$

Decision rule (conceptual):

If D(t) > D critical, the system transitions into a pre-bifurcation or collapse regime, characterized by loss of homeostasis, increased instability, and elevated biological risk.

3.4 Parameterization and biological plausibility

Parameter ranges are selected to reflect general timescales and qualitative behavior reported for mitochondrial dysfunction: changes in ΔΨm and ROS dynamics can occur on minutes-to-hours timescales, whereas network remodeling via fusion/fission and quality-control feedback can evolve over similar experimental timescales [4]–[6]. Importantly, values are not calibrated to any specific disease, toxin, or agent, but rather to broad orders of magnitude consistent with the literature on mitochondrial stress responses. This preserves generality and supports dual-use safety-by-design.

3.5 Data linkage and future calibration (non-operational)

Future work may calibrate and validate the framework using structured *in vitro* datasets (e.g., mitochondrial membrane potential (ΔΨm), reactive oxygen species (ROS), and mitochondrial morphology metrics obtained under controlled stress conditions), as well as cybrid or engineered cell systems with defined mtDNA variants to validate the dynamics of μ(t). This would enable integration into "digital twin" pipelines without encoding agent-specific or operational details [2], [10].

3.6 Statistics and Simulation

The coupled coarse-grained ODE system for mitochondrial connectivity M(t), membrane potential Ψ(t), reactive oxygen species R(t), and heteroplasmy μ(t) was numerically integrated over $t \in [0, 200]$ (arbitrary units) using an adaptive Runge–Kutta solver (RK45) with strict tolerances (rtol = 10^-7, atol = 10^-9). Initial conditions were set to M0 =

0.90, Ψ0 = 0.90, R0 = 0.20, and μ0 = 0.05. To ensure stable integration and reproducibility, the ROS production term proportional to 1/Ψ(t) was regularized via Ψ_eff = max(Ψ(t), ε) with ε = 10^-2. Early-warning statistics can be computed from the simulated trajectories using rolling-window indicators (e.g., rolling variance and lag-1 autocorrelation) with a 20-unit window; these provide quantitative proxies for variance inflation and critical slowing down in pre-bifurcation regimes without mapping the abstract stress variable to any concrete experimental intervention.

4 Results

4.1 Typical dynamic regimes

Simulations reveal three qualitative regimes:

Table 1. Regimes of mitochondrial network dynamics

Regime	**ΔΨm (Ψ)**	**ROS (R)**	**Network Connectivity (M)**	**Heteroplasmy (μ)**	**Interpretation**
Homeostatic	High	Moderate	High	Stable, low	Normal mitochondrial function
Pre-bifurcation	Decreasing	Increasing	Decreasing	Accelerated increase	Elevated risk /early-warning regime
Collapse	Near zero	Very high	Near zero	Dominant mutant fraction	Systemic mitochondrial failure

These regimes are consistent with the view that mitochondrial networks may exhibit tipping-point behavior near criticality, where small changes in effective stress or feedback can produce significant functional shifts [7].

4.2 Early-warning indicators

Prior to collapse, the model produces characteristic defensive "early-warning" signatures: (i) critical slowing down in the recovery of Ψ(t), (ii) increasing variance and oscillatory behavior in R(t), and (iii) destabilization and progressive fragmentation of the mitochondrial network, reflected in M(t). These signatures align conceptually with near-critical behavior and provide a basis for designing monitoring thresholds and resilience metrics [7].

The structure of the proposed model can be conceptualized as a set of coupled feedback interactions among mitochondrial network connectivity (M), membrane potential (Ψ), reactive oxygen species (R), and mtDNA heteroplasmy (μ). Network connectivity positively supports membrane potential stability, while declining membrane potential promotes ROS generation through increased electron leakage. Elevated ROS levels, in turn, negatively affect both membrane potential and network integrity, reinforcing a destabilizing feedback loop. Mitochondrial fusion and fission modulate these interactions by influencing both network structure and the segregation or complementation of mutant mtDNA. An abstract stress input A(t) acts as a system-level perturbation that amplifies existing internal stresses without representing any specific biological agent or intervention.

Within this coupled framework, the system exhibits distinct qualitative dynamic regimes. In the homeostatic regime, high network connectivity and stable membrane potential are maintained, ROS levels remain moderate, and heteroplasmy stays low. As stress accumulates, the system may enter a pre-bifurcation regime characterized by a gradual loss of membrane potential, increased variability in ROS levels, progressive network fragmentation, and accelerated changes in heteroplasmy. This intermediate regime represents an elevated-risk state in which early-warning indicators become detectable. If destabilizing feedbacks dominate, the system transitions into a collapse regime marked by near-complete loss of membrane potential and network connectivity, excessive ROS accumulation, and dominance of mutant mtDNA, corresponding to systemic mitochondrial failure.

The transition between these regimes can be interpreted through a threshold-based perspective, in which a composite risk index captures the balance between stabilizing and destabilizing processes. Exceeding a critical threshold signals proximity to a bifurcation point and loss of homeostasis, providing a conceptual basis for early-warning monitoring and resilience-oriented assessment rather than predictive or exploitative control.

5 Discussion

5.1 Dual-use implications and safety-by-design

Contemporary dual-use AI governance emphasizes assessing "capability thresholds" and whether a model meaningfully enables high-consequence misuse [2]. This work is intentionally designed to remain below such thresholds. Specifically, the framework:
(i) uses an abstract input A(t) not tied to any real agent/protocol;
(ii) avoids parameterization against specific toxins, pathogens, concentrations, or lab workflows;
(iii) focuses on early warning and resilience rather than optimization of disruption.
Accordingly, the model provides insight without capability, supporting risk awareness and resilience engineering without generating operational exploitation knowledge—consistent with best practices for dual-use-aware modeling [2].

5.2 Cyberbiosecurity and national security relevance

Cyberbiosecurity highlights that modern biology is increasingly cyber-physical and therefore vulnerable to hybrid disruptions at the interface of computation and life sciences [3], [8]. Within this landscape, non-exploitative quantitative models can support stress testing of biological resilience, evaluation of monitoring thresholds, and the design of early-warning indicators to protect biomedical infrastructure. Positioning biological stability as a component of critical infrastructure further motivates the use of defense-oriented modeling as a strategic analytical asset [8], [11].

5.3 Biomedical benefits

Because tipping points and instability regimes are relevant to mitochondrial disease and broader degenerative pathophysiology, a regime-based model can also inform biomedical monitoring strategies and resilience interventions that target network dynamics (e.g., improving antioxidant capacity, modulating fusion/fission balance) without specifying harmful triggers [4]–[7].

5.4 ERP interpretation as resilience mapping

ERP suggests that health depends on maintaining energy transformation within an optimal resistance/flux zone [9]. Our framework provides a quantitative method for mapping departures from stable zones via early-warning indicators (declining $\Psi(t)$, rising/oscillatory ROS, fragmentation), thereby reinforcing a resilience-oriented interpretation while remaining non-operational.

6 Conclusion

This paper demonstrates that computational modeling of mitochondrial networks can be scientifically informative while being ethically and operationally constrained for dual-use risk management. By using an abstract, agent-agnostic stress input A(t), focusing on dynamic regimes and early-warning indicators, and avoiding protocol- or compound-specific operational details, the framework supports risk assessment, resilience engineering, and early warning without increasing exploitative capabilities.
Next steps include formal integration with dual-use AI risk governance (pre-specified thresholds, evaluation protocols, and red-teaming focused on unintended capability emergence) in line with current guidance for biological AI models [2]. Multi-scale extensions could link cell-level trajectories to tissue- and organ-level resilience indicators in digital-twin contexts, thereby enhancing defensive utility while preserving safety-by-design.

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Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

The authors contributed equally to the present research at all stages, from the formulation of the problem to the final findings and solution.

Sources of Funding for Research Presented in a Scientific Article or Scientific Article Itself

No funding was received for conducting this study.

Conflict of Interest:

Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.