Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ31485

A New Model Focused on Apoptosis-Induced Proliferation and Compensatory Proliferation of the General Process of Cell Apoptosis and Proliferation

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Abstract. Cells are essential for every living organism, and the balance between cell apoptosis and cell proliferation is critical for cells to be healthy. Traditional apoptosis–proliferation models typically represent proliferation as a single aggregated term, failing to distinguish the biological mechanisms underlying regenerative growth. This study constructs an ordinary differential equation (ODE) model to explicitly separate two key regenerative mechanisms: apoptosis-induced proliferation (AIP) and compensatory proliferation (CP). AIP (Apoptosis-induced Proliferation) is triggered when apoptotic cells undergo death, secreting signals that stimulate the cell cycle in adjacent proliferative cells. CP (Compensatory Proliferation), by contrast, is triggered based on tissue size. AIP is more rapid but less stable than CP. Python was used to simulate three different conditions for a human thymus: healthy condition, injured condition, and tumor growth condition. The total cells, proliferative cells, apoptotic cells, and rate of AIP and CP were graphed. Results demonstrated that AIP induces more rapid cell growth but is unstable and may promote tumorigenesis, while CP is more stable in increasing cell numbers to reach tissue capacity. This model provides a quantitative tool for distinguishing pathological from physiological proliferation, exhibiting clear translational potential in cancer-targeted therapy and regenerative medicine, particularly in inhibiting AIP-driven malignant progression of tumors.

Keywords: Apoptosis-induced Proliferation, Compensatory Proliferation, Ordinary Differential Equation

1. Introduction

Cell apoptosis is a process of programmed cell death. This process eliminates non-functional or potentially harmful cells. Without such programmed death, aberrant cells remain in the body and increase the risk of cancer and uncontrolled proliferation. However, excessive or inappropriate apoptosis can lead to diseases such as Parkinson's and Alzheimer's, resulting in tissue degeneration and atrophy. Importantly, apoptotic cells are not merely removed from tissues but can actively stimulate neighboring cells to proliferate through apoptosis-induced proliferation (AIP), a mechanism that plays a key role in tissue maintenance and regeneration. Cell proliferation (CP) is a

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process of cells reproducing themselves. This ensures tissue growth and regeneration. The cell division from the cell cycle mechanism is an example of the CP, where a parent cell divides into two daughter cells. In addition to baseline proliferation, tissues employ CP to restore cell numbers following injury or cell loss, thereby preserving tissue integrity. The balance between cell apoptosis and proliferation is critical for maintaining human health. Disorders happen when the balance between them is disrupted.

AIP is a regenerative process where dying cells release mitogenic signals (e.g., via the JNK pathway) to activate growth factors like Wingless/Wnt, Hedgehog, and DPP/BMP, driving nearby cell proliferation. This mechanism enables rapid tissue repair post-injury but lacks intrinsic size control. Persistent apoptotic signaling can cause uncontrolled cell turnover, elevating risks of hyperproliferation and tumor progression. CP is a regenerative mechanism in which surviving cells proliferate to restore tissue size after cell loss. Unlike AIP, CP is not triggered by apoptotic signaling but responds to changes in tissue size or density. CP generally operates more slowly than AIP but is more stable. As tissue size approaches its normal capacity, CP-driven proliferation decreases and ultimately ceases, preventing excessive growth. This capacity-dependent regulation makes CP essential for long-term tissue homeostasis and controlled regeneration.

Although the biological mechanisms of AIP and CP have been characterized individually, existing mathematical models often treat proliferation as a single aggregate term, failing to distinguish the differential contributions of these two processes to tissue homeostasis, injury repair, and tumorigenesis. The objective of this study is to develop an ODE-based model that explicitly distinguishes apoptosis-induced proliferation and compensatory proliferation. The questions addressed are: How do AIP and CP differ in their effects on tissue recovery and stability? Under what conditions does AIP promote rapid regeneration versus pathological overgrowth? How does CP regulate proliferation to restore tissue size without exceeding carrying capacity? This framework enables quantitative comparison of physiological regeneration and pathological proliferation.

2. Literature review

The dynamic balance between cell proliferation and apoptosis is a fundamental principle governing tissue homeostasis, regeneration, and disease progression. Early mathematical studies treated cell populations as relatively homogeneous systems in which proliferation and death compete to determine net growth [1]. Hardy and Stark's model, though foundational, oversimplifies proliferation by treating it as a homogeneous process, ignoring the distinct roles of AIP and CP.

While early models focused on homogeneous cell populations, subsequent studies revealed the complexity of regeneration mechanisms. AIP has been documented across multiple organisms and tissue types [2]. Different from a subtractive process, Ryoo and Bergmann showed that apoptotic cells emit mitogenic signals that stimulate proliferation in neighboring cells, directly coupling cell death to regenerative growth. This paradigm shift established apoptosis as a signaling event. Mechanistic studies have identified the JNK pathway as a key driver of AIP, triggering the release of growth factors like Wingless/Wnt, Hedgehog, and Dpp/BMP., which drive adjacent cells into the cell cycle [3]. Bergmann and Fan further clarified the distinction between AIP and other regenerative processes by emphasizing that AIP is local, rapid, and signal-driven, but may be unstable when chronically activated. AIP has been implicated in cancer progression, where sustained apoptotic signaling can exert selective pressure for apoptosis-resistant, hyper-proliferative clones. Studies integrating biological experiments with mathematical modeling have shown that CP acts as a stabilizing feedback mechanism that regulates growth toward a target tissue size or carrying capacity

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[4]. In cancer studies, CP-related feedback loops have been proposed as potential therapeutic targets, as disrupting these homeostatic signals may limit tumor regrowth after treatment-induced cell death.

Despite extensive biological characterization, few mathematical models explicitly distinguish between AIP and CP, restricting their capacity to analyze the individual contributions of these mechanisms to tissue stability [5,6]. Many cancer and regeneration models incorporate apoptosis-stimulated growth or density-dependent proliferation, but rarely categorize them into mechanistically interpretable terms. This lack of categorization limits the ability to analyze their individual contributions to stability, overshoot, and long-term tissue behavior. The present study addresses this gap by extending classical ODE-based population models to explicitly include distinct AIP and CP-driven proliferation terms. The model enables direct comparison of rapid, apoptosis-triggered regeneration versus slower, capacity-driven homeostatic control. This explicit separation represents a key novelty of the work and provides a mathematically transparent framework for exploring how differential regulation of AIP and CP may contribute to regeneration, cancer progression, and degenerative diseases.

3. Mathematical model development

Original ODE Model

In Hardy and Stark's research, their ODE model does not include AIP and CP and is simply written as rate of change of cells x with time t = rate of production of new cells - rate of death of cells.

$$\frac{dx}{dt} = \gamma x - \alpha x^2 \tag{1}$$

proliferation rate = γ and apoptosis rate = α

A new model is required to explicitly distinguish between AIP and CP.

New Model

P(t) = number of proliferative cells at time t

A(t) = number of apoptotic cells at time t

$$\frac{dP}{dt} = \beta P + \gamma A + \delta(K - P - A) - \alpha P \tag{2}$$

Rate of change of proliferative cells = baseline proliferation + AIP + CP- baseline loss

γA represents the increase by AIP and δ(K−P−A) is for CP, K denotes the carrying capacity, and K-P-A quantifies the remaining capacity relative to the carrying capacity K. αP is the rate of proliferative cells transform to apoptotic cells.

$$\frac{dA}{dt} = \alpha P - \lambda A \tag{3}$$

Rate of change of apoptotic cells = baseline apoptosis - clearance of apoptotic cells

λA is the rate of apoptotic cell clearance.

Combining the equations for proliferative and apoptotic cells enables simulation of the rate of change of total cell number, where total cell number.

$$N(t) = P(t) + A(t) \tag{4}$$

Simulations were conducted for human thymus cells with the following parameter values:

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$\alpha = 0.5$ - basal apoptosis rate
$\beta = 0.5$ - basal proliferation rate
$\gamma = 0.3$ - AIP coefficient
$\delta = 1.3$ - CP coefficient
$\lambda = 24$ - apoptotic cell clearance rate
$K = 10000$ - carrying capacity

The parameter values employed were chosen for biological plausibility and consistency with reported ranges in experimental and modeling studies of human tissues. The basal apoptosis rate ($\alpha = 0.5$) and basal proliferation rate ($\beta = 0.5$) represent balanced turnover under homeostatic conditions, a common assumption in classical apoptosis–proliferation models where steady-state tissue size is maintained when proliferation and death rates are balanced [1]. Similar relative magnitudes for proliferation and apoptosis rates have been used in prior ODE-based models of tissue homeostasis and cancer growth [7].

The apoptosis-induced proliferation coefficient ($\gamma = 0.3$) reflects the experimentally observed coupling between apoptotic signaling and short-range proliferative responses mediated by pathways such as JNK and Wnt signaling [3]. This value was chosen to be smaller than the basal proliferation rate, consistent with evidence that AIP acts as a modulatory rather than dominant growth mechanism under physiological conditions. The compensatory proliferation coefficient ($\delta=1.3$) was selected to represent a strong but self-limiting regenerative response when tissue size is far below carrying capacity, as observed in organ regeneration processes such as liver regrowth following partial hepatectomy [4].

The apoptotic cell clearance rate ($\lambda=24$) reflects the rapid removal of apoptotic cells by macrophages and dendritic cells, which typically occurs on the order of hours rather than days [2]. This fast clearance is essential for maintaining low steady-state apoptotic cell numbers in healthy tissue. The carrying capacity ($K=10,000$) represents a normalized tissue size and is used to scale population dynamics rather than to represent an absolute cell count.

Model validation was conducted at both steady-state and dynamic levels. First, steady-state behavior was examined under healthy conditions to confirm that the model maintains a stable equilibrium near the carrying capacity when apoptosis, proliferation, AIP, and CP are balanced. This behavior is consistent with established theoretical models of tissue homeostasis [6].

Second, dynamic responses were evaluated by simulating injury and recovery scenarios and comparing qualitative trends with experimental observations from regenerative tissues. In particular, the model's recovery dynamics resemble liver regeneration following partial hepatectomy, where rapid early proliferation is followed by gradual stabilization as tissue size approaches its original level [4]. The ability of the model to reproduce rapid initial growth, followed by saturation without overshoot when CP dominates, supports its biological plausibility.

Finally, pathological validation was conducted by reducing apoptotic cell clearance, leading to sustained AIP activation and uncontrolled growth. This behavior is consistent with experimental and theoretical studies linking impaired apoptotic clearance and chronic death signaling to tumor progression [7]. Collectively, these validation approaches demonstrate that the model captures both physiological and pathological proliferation dynamics.

In the graphs, The blue line represents the number of Proliferating Cells(P), the red line represents the number of Apoptotic Cells(A).The purple line represents the total amount of cells (P+A). The green line represents the AIP Rate(γA) and the brown line represents the CP Rate($\delta(K-P-A)$).

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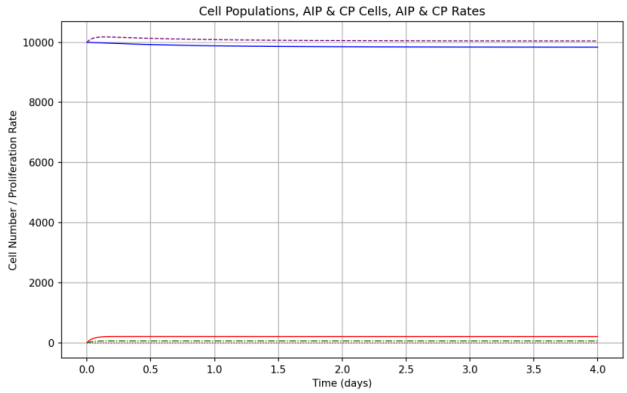

Figure 1. Normal healthy human thymus cells simulation

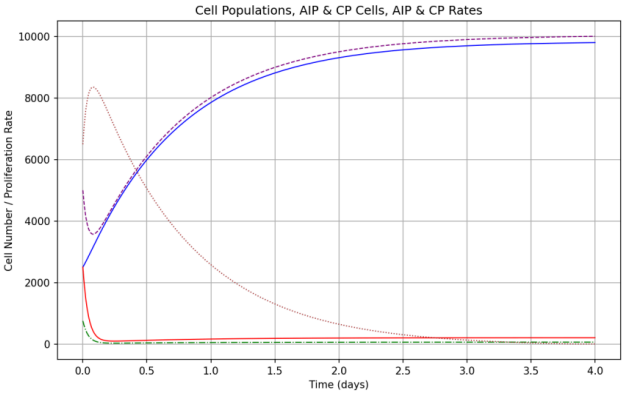

Figure 2. Injured human thymus cells recovering to healthy

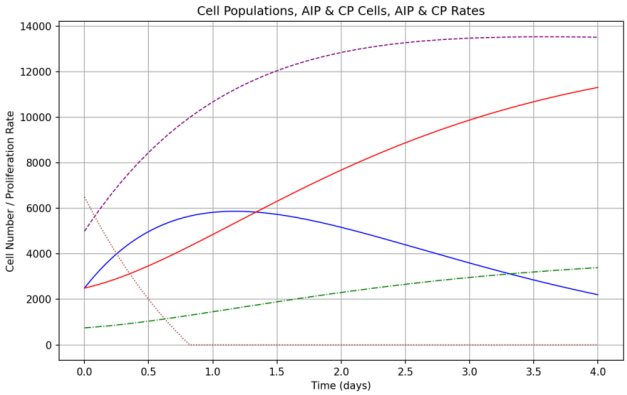

Figure 3. Thymus tumor (thymomas/carinomas) formation

4. Analysis

In Figure 1, the simulation of a healthy human thymus exhibits stable dynamics, with both AIP and CP rates maintained at baseline levels. Proliferative and apoptotic cell populations remain stable, and the total cell number reaches and maintains the carrying capacity. Rapid apoptotic cell clearance by macrophages and immature dendritic cells ensures that most cells remain proliferative. Quantitatively, the rates of change for proliferative cells (dP/dt) and apoptotic cells (dA/dt) fluctuate minimally around zero, indicating near-zero net growth and a balanced homeostatic state.

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Figure 2 illustrates recovery from thymic injury, where initial proliferative and apoptotic populations are each one-fourth of their carrying capacity. Early in recovery, the high number of apoptotic cells transiently elevates AIP, accounting for approximately 10% of the net proliferation rate at the initial time points. CP dominates the later recovery phase, driving proliferation in response to the tissue capacity deficit. The contribution of CP peaks when total cell number is far below carrying capacity and gradually decreases to zero as the tissue approaches carrying capacity. This dynamic can be quantified by tracking the relative contributions of AIP and CP to dP/dt over time, confirming that CP is the primary mechanism restoring cell numbers in the long term.

Figure 3 shows the formation of a thymus tumor under impaired apoptotic clearance ($\lambda = 0$). Initial conditions are consistent with those in Figure 2, but the inability to remove apoptotic cells leads to a sustained increase in AIP activity. The contribution of AIP to the net proliferation rate continuously increases during the tumor growth phase, whereas CP contributes only when total cell numbers are below the carrying capacity. The final effect is uncontrolled proliferation, with total cells exceeding the nominal capacity and apoptotic cells accumulating, illustrating how loss of clearance destabilizes tissue homeostasis and drives pathological growth.

5. Discussion

The mathematical model presented in this study established a mechanistic framework to distinguish between AIP and CP, capturing their individual contributions and distinct effects on tissue dynamics through simulations under different conditions. AIP, triggered by apoptotic cells, is rapid and localized, providing immediate stimulation to adjacent proliferative cells. This is particularly evident in the early recovery phase following injury, where apoptotic signals transiently accelerate proliferation. However, simulations also indicate that dysregulated AIP can destabilize tissue homeostasis, as observed in Figure 3, where a lack of apoptotic clearance led to uncontrolled growth and tumor formation. These findings are consistent with experimental observations that chronic AIP activation can drive hyperproliferation and cancer progression [2,3]. CP, by contrast, is a tissue-level feedback mechanism that adjusts proliferation according to available capacity. Its stabilizing influence is apparent in the recovery of injured tissue, where CP ensures that proliferative activity gradually restores cell numbers to the carrying capacity without overgrowth. This model demonstrates that CP is less sensitive to immediate apoptotic signals but critical for long-term maintenance of tissue homeostasis, aligning with previous reports on liver regeneration and other organ repair processes [5,8].

By incorporating explicit terms for both AIP and CP, this model enables exploration of scenarios that cannot be captured by conventional ODE models which aggregate all proliferative responses into a single term [1,6]. Additionally, the model offers potential utility for studying regenerative therapies and degenerative diseases, providing a quantitative platform for evaluating how modulation of AIP or CP could influence recovery outcomes.

Despite its ability to distinguish between AIP and CP, the present model has several limitations. The framework assumes homogeneous cell populations and does not account for cellular heterogeneity, such as differences between stem cells, progenitor cells, and differentiated cells, which may influence proliferation and apoptotic responses. Model parameters were selected based on population-averaged values reported in the literature, and individual variability associated with age, genetic background, or disease state was not incorporated. In addition, the model focuses on intrinsic tissue dynamics and does not include feedback from the immune microenvironment; immune cells such as T cells and macrophages are known to regulate apoptotic clearance and regenerative signaling, and may substantially affect tissue outcomes. Future extensions could

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address these limitations by incorporating spatially discretized or agent-based formulations to capture local cell–cell interactions and clustering effects, as well as by applying machine learning approaches to improve parameter estimation and model calibration by applying experimental or clinical data. Finally, extending the model to include multiple proliferative subpopulations, such as stem cells and progenitor cells, would provide a more detailed representation of tissue hierarchy and improve the model's applicability to cancer progression, regenerative medicine, and therapeutic response modeling [9,10].

6. Conclusion

This study establishes an ODE-based model that explicitly distinguishes between AIP and CP, providing insights into their distinct roles in tissue dynamics. Simulations demonstrate that AIP facilitates rapid, signal-driven proliferation in response to apoptotic events, whereas CP ensures long-term tissue stability by responding to capacity deficits. The interplay between these mechanisms governs tissue homeostasis, regeneration, and, under pathological conditions, tumorigenesis. By clarifying the contributions of AIP and CP, this model establishes a foundation for further research into regenerative medicine, cancer biology, and tissue engineering. Future work may refine the model to incorporate spatial, stochastic, and pathway-specific dynamics, enabling more precise predictions of tissue behavior under diverse physiological and pathological scenarios to help research in tumor growth and cancer.

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