# Bistable dynamics of TAN-NK cells in tumor growth and control of radiotherapy-induced neutropenia in lung cancer treatment.

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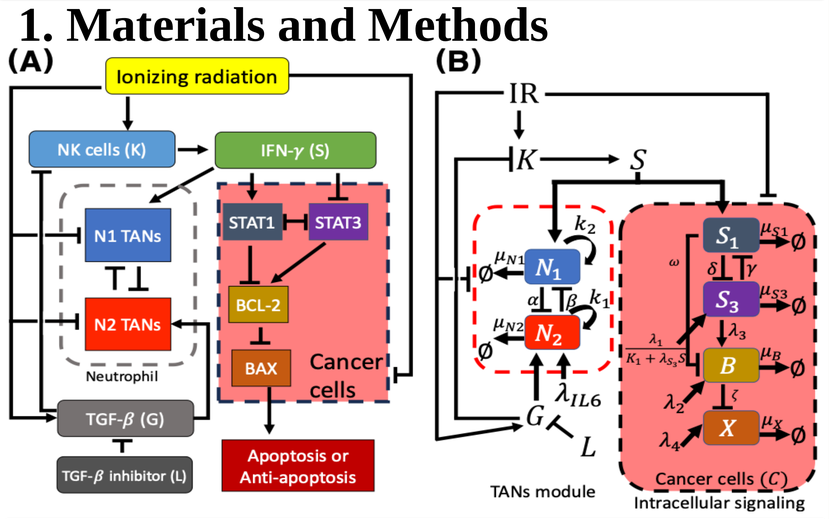
Neutrophils play a crucial role in the innate immune response as a first line of defense in many diseases, including cancer. Tumor-associated neutrophils (TANs) can either promote or inhibit tumor growth in various steps of cancer progression via mutual interactions with cancer cells in a complex tumor microenvironment (TME). In this study, we developed and analyzed mathematical models to investigate the role of natural killer cells (NK cells) and the dynamic transition between N1 and N2 TAN phenotypes in killing cancer cells through key signaling networks and how adjuvant therapy with radiation can be used in combination to increase anti-tumor efficacy. We examined the complex immune-tumor dynamics among N1/N2 TANs, NK cells, and tumor cells, communicating through key extracellular mediators (Transforming growth factor (TGF-β), Interferon gamma (IFN-γ)) and intracellular regulation in the apoptosis signaling network. We developed several tumor prevention strategies to eradicate tumors, including combination (IFN-γ, exogenous NK, TGF-βinhibitor) therapy and optimally-controlled ionizing radiation in a complex TME. Using this model, we investigated the fundamental mechanism of radiation-induced changes in the TME and the impact of internal and external immune composition on the tumor cell fate and their response to different treatment schedules.

## 1. Materials and Methods

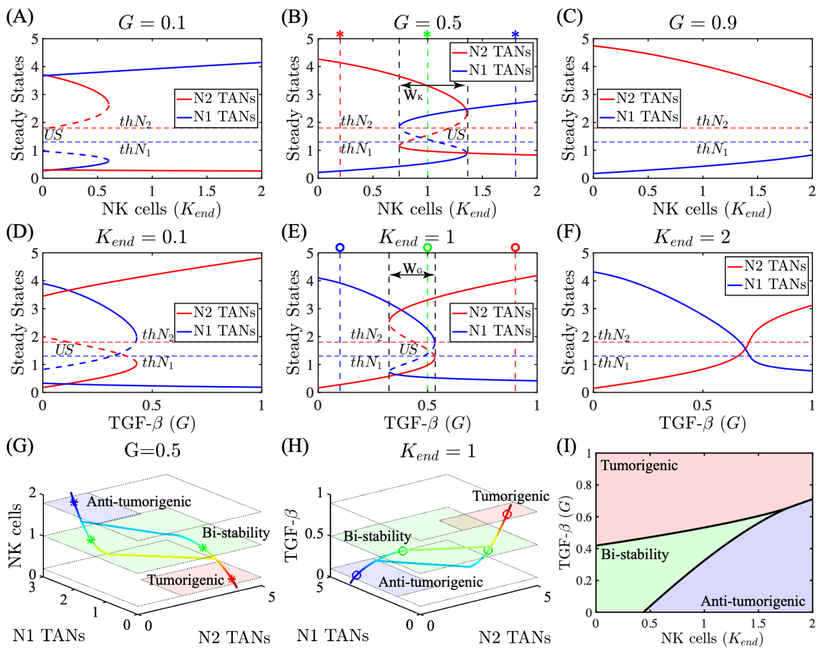



- $\frac{dN_2}{dt} = \lambda_6 + \lambda_G G + \frac{k_1 k_2^2}{k_2^2+\alpha N_1^2} - \mu_{N2} N_2 - \epsilon_{N2}\mu_{RT} N_2$
- $\frac{dN_1}{dt} = \lambda_{S1} S + \frac{k_3 k_4^2}{k_4^2+\beta N_2^2} - \mu_{N1} N_1 - \epsilon_{N1}\mu_{RT} N_1$
- $\frac{dG}{dt} = \lambda_C C - \gamma_L L G - \mu_G G + \lambda_{RG}\mu_{RT}$
- $\frac{dL}{dt} = u_L - \mu_L L$
- $\frac{dS}{dt} = u_S + \lambda_K K_{end} + \lambda_{K'} K_{ex} - \mu_S S$
- $\frac{dK_{end}}{dt} = \lambda_{NK} + \frac{k_5 k_6^2}{k_6^2+\theta G^2} - \mu_K K_{end} + \lambda_{RK}\mu_{RT}$
- $\frac{dK_{ex}}{dt} = u_K - \mu_{K'} K_{ex}$
- $\frac{dS_1}{dt} = \lambda_{S2} S + \frac{a_1 a_2^2}{a_2^2+\gamma S_3^2} - \mu_{S1} S_1$
- $\frac{dS_3}{dt} = \frac{\lambda_1}{K_1+\lambda_{S3} S} + \frac{a_3 a_4^2}{a_4^2+\delta S_1^2} - \mu_{S3} S_3$
- $\frac{dB}{dt} = \lambda_2 + \frac{a_5 a_6^2}{a_6^2+\omega S_1^2} + \lambda_3 S_3 - \mu_B B$
- $\frac{dX}{dt} = \lambda_4 + \frac{a_7 a_8^2}{a_8^2+\zeta B^2} - \mu_X X$
- $\frac{dT}{dt} = rC\left(1-\frac{T}{T_0}\right) - \delta_1 N_1 C - \delta_2 C I_{apop} - \delta_3 C(K_{end}+K_{ex}) - \mu_{RT} C$

*Blue : considering radiation therapy.

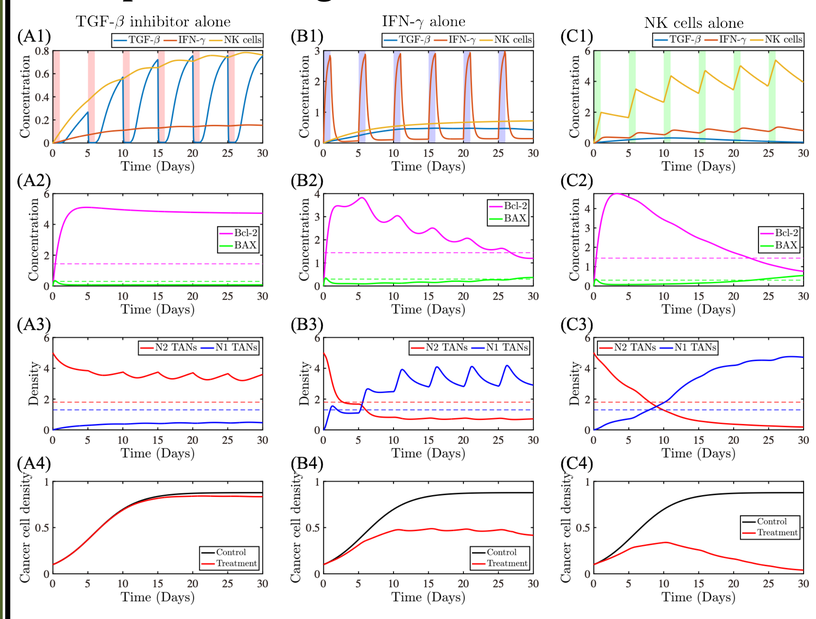
## 2. Results

### Bifurcation diagram

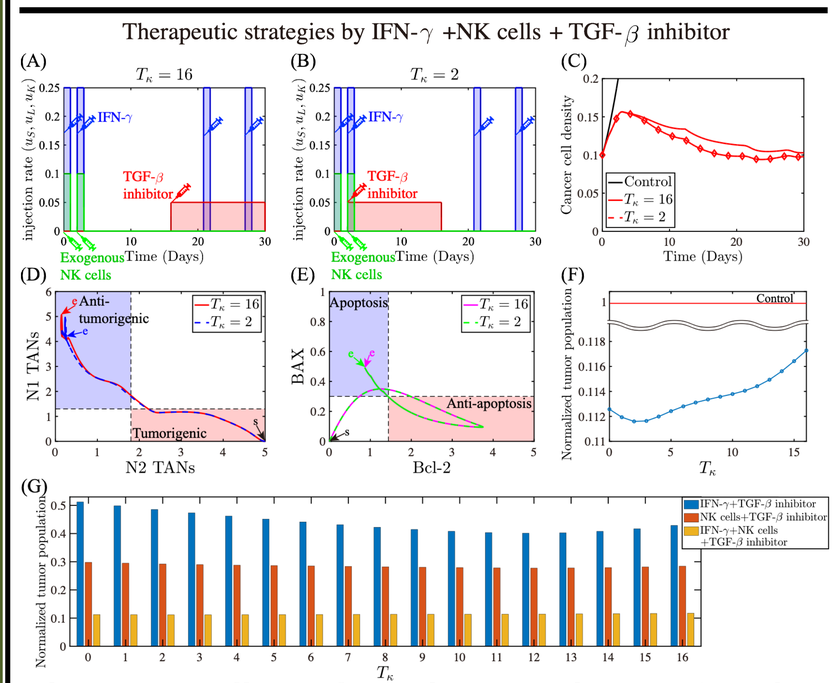



Bifurcation diagram for N1 and N2 TANs w.r.t. NK cell signal and TGF-beta.

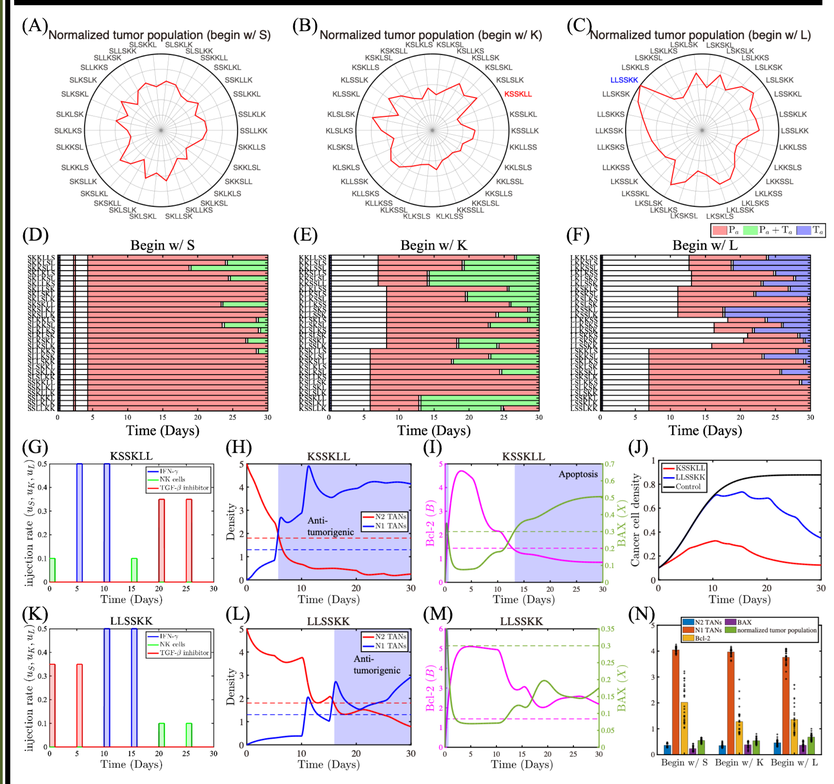
## Therapeutic strategies




Therapeutic effect of the TGF-beta inhibitor, IFN-gamma, exo-NK cells.




Therapeutic effect of combination therapy (TGF-beta inhibitor, IFN-gamma, exo-NK cells).

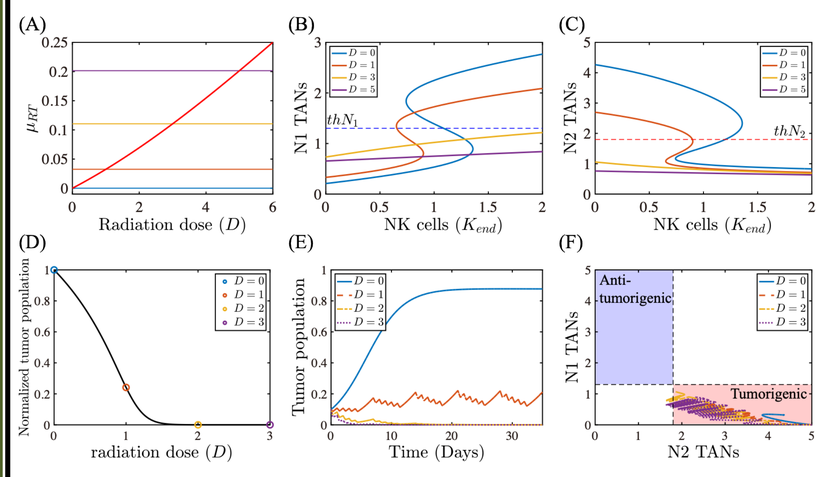



Maximizing anti-tumor efficacy.

## 3. Radiotherapy

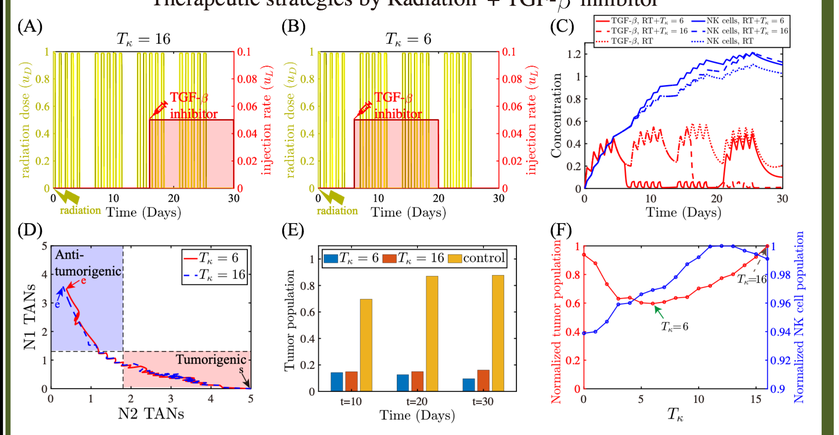
### Linear-quadratic (LQ) model

$$\mu_{RT} = \mu_0\left(1 - e^{-\alpha_{RT} D - \beta_{RT} D^2}\right)$$



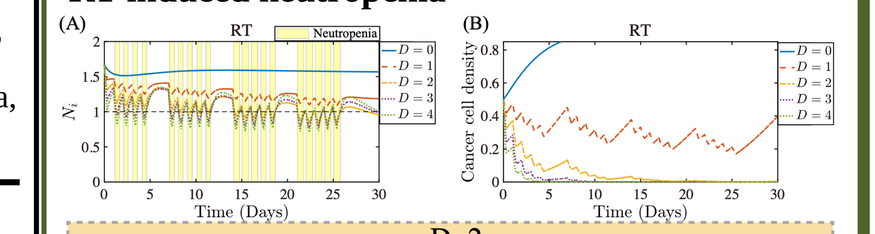

Therapeutic effect of radiation in early stage.

## Therapeutic strategies by Radiation + TGF-$\beta$ inhibitor




Therapeutic effect of radiation therapy and TGF-beta inhibitor.

## RT-induced neutropenia

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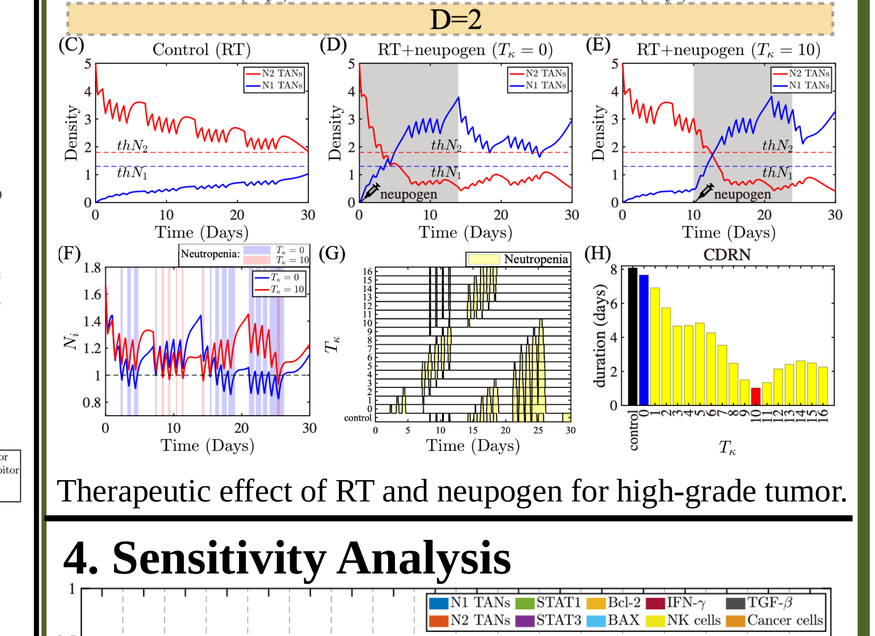
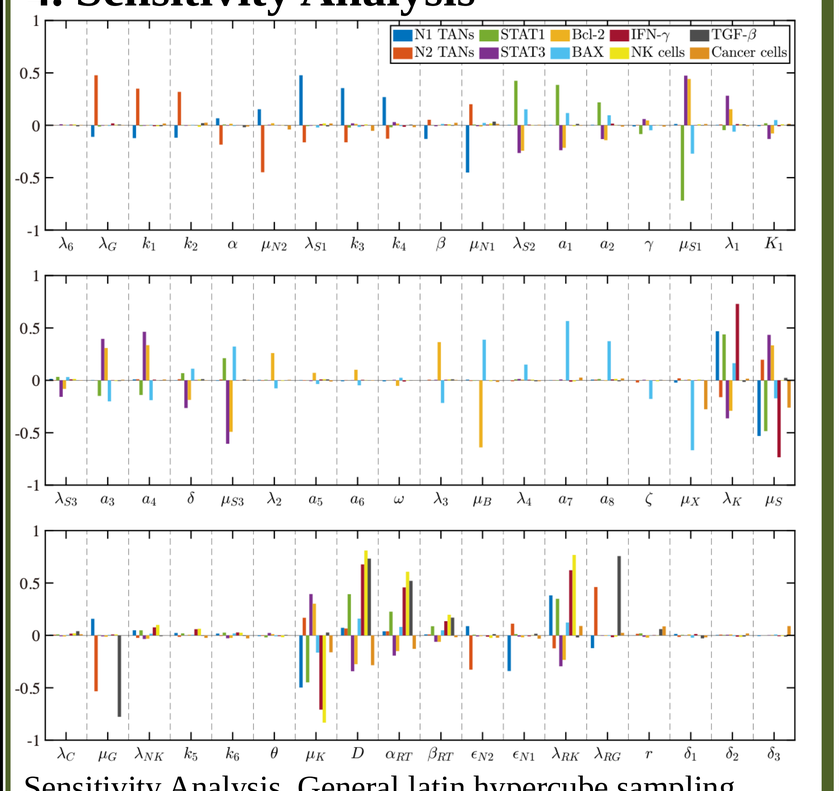



Therapeutic effect of RT and neupogen for high-grade tumor.

## 4. Sensitivity Analysis




Sensitivity Analysis. General latin hypercube sampling scheme and partial rank correlation coefficient (PRCC) with a sample size 10,000.

## 5. Conclusions

This work should be a starting point of finding the fundamental mechanism of biochemical interactions of N1/N2 TANs-tumor-NK cells. In the TME, there are many other critical factors that we did not consider in this work, such as M1/M2 TAMs, signaling networks, angiogenesis, tumor-associated fibroblasts, tumor ECM remodeling and restructuring, CSF-1, and NET which can also play a pivotal role in regulation of cancer progression. In addition, mutations in STAT1 and STAT3 molecules (loss of function (LOF) or gain of function (GOF)) were not considered. While we focused on TANs due to their rapid phenotypic plasticity and influence on tumor-immune interactions [15], M1/M2 TAMs are another critical component of the tumor microenvironment. Both TAMs and TANs contribute to immunosuppressive and pro-tumorigenic pathways, often governed by overlapping cytokines such as TGF-βand IL-6.

## 6. References

1. J. Lee, D. Lee, and Y. Kim, Mathematical model of STAT signalling pathways in cancer development and optimal control approaches, Royal Society Open Science, 8, 210594, 2021.
2. Y. Kim, D. Lee, J. Lee, S. Lee, and S. Lawler, Role of tumor-associated neutrophils in regulation of tumor growth in lung cancer development: A mathematical model, PLoS One, 14, e0211041, 2019.