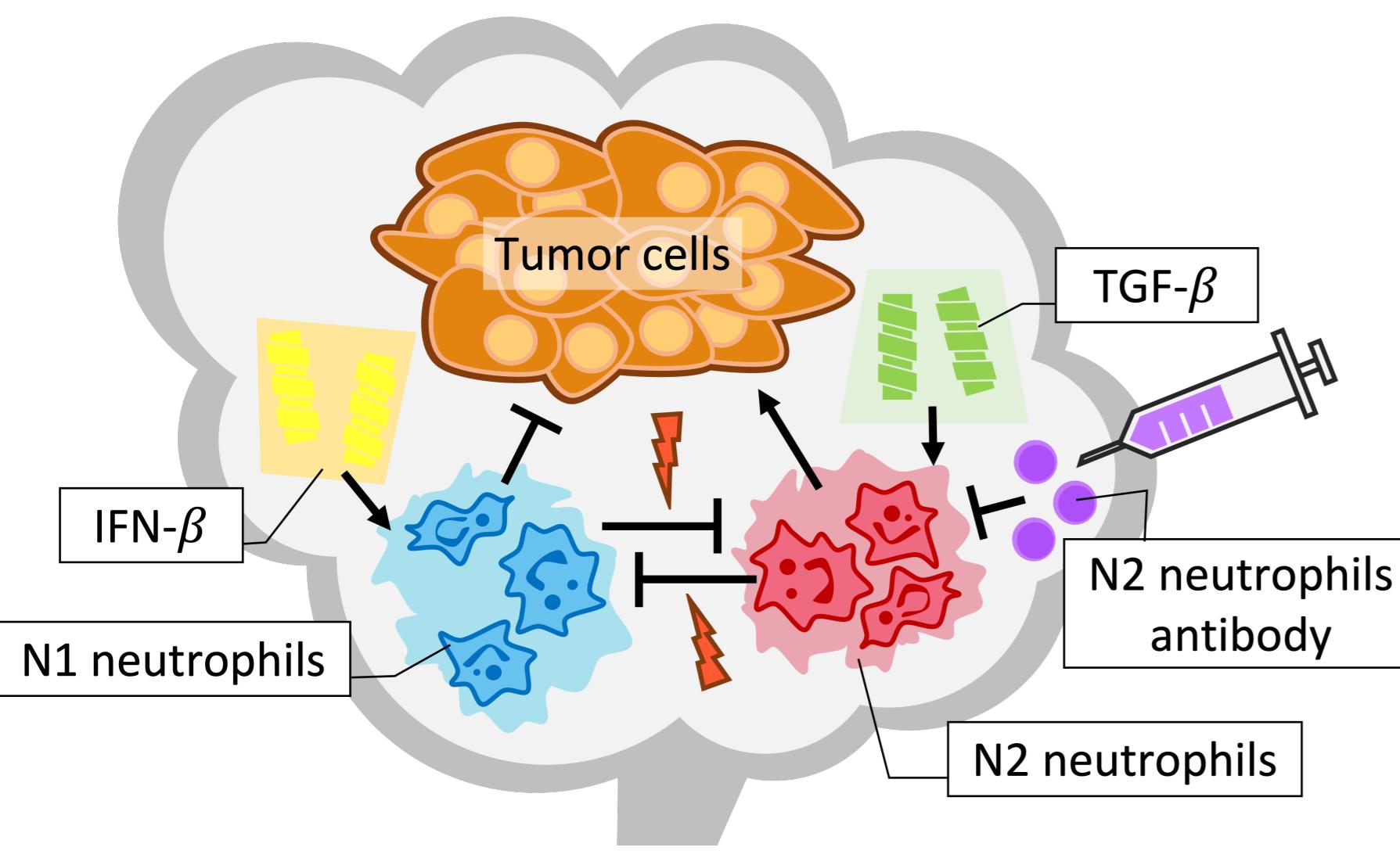




Effect on tumor growth in systems of two different types of tumor-associated neutrophils : A mathematical model

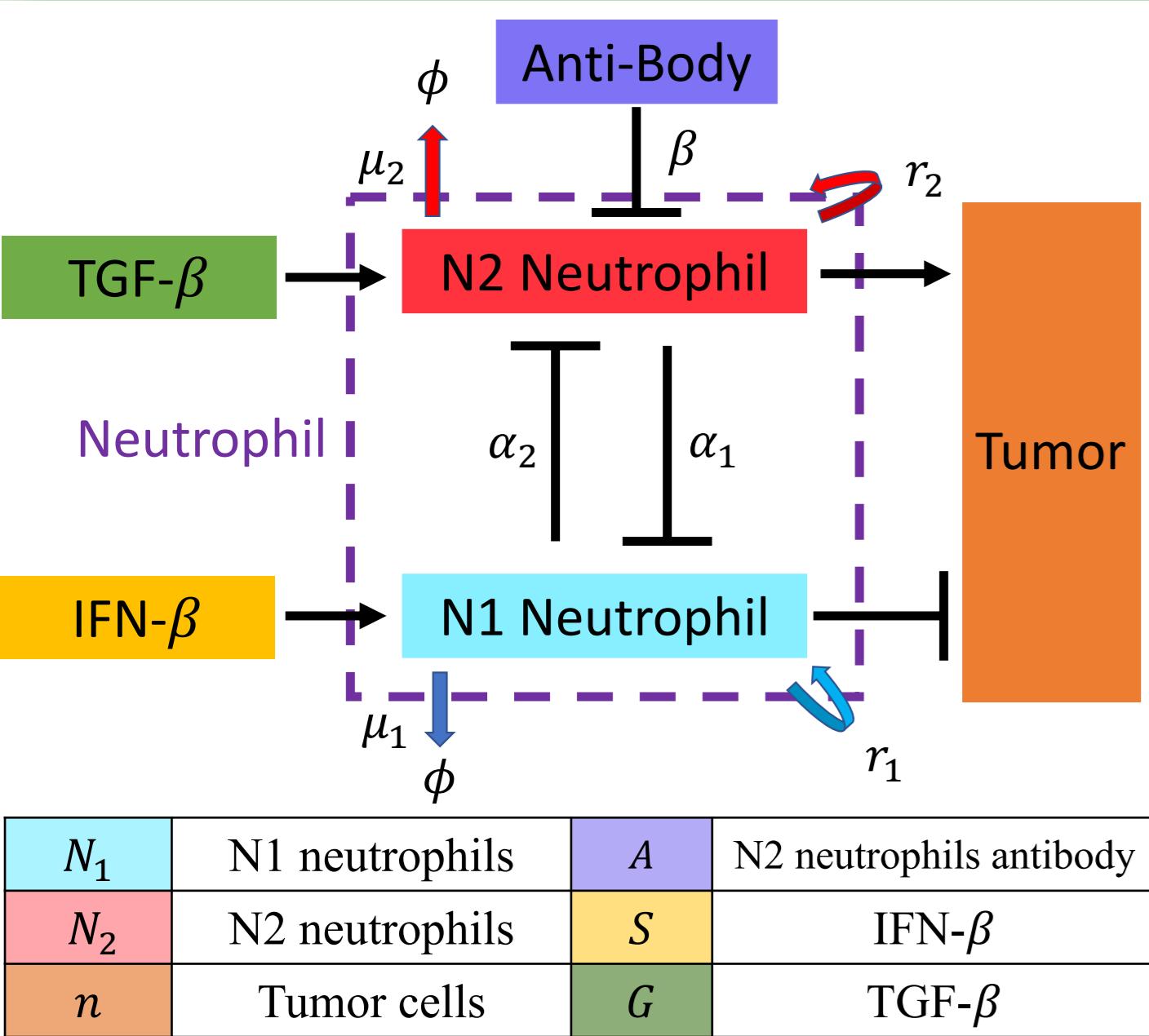


1. Introduction



Tumor-associated neutrophils (TANs) have been under discussion for their dual role on tumor microenvironment, but they are emerging as important agents in tumor invasion. In this study, we divided TANs into two different phenotypes: N1 TANs, the anti-tumor neutrophils and N2 TANs, the tumorigenic neutrophils. We developed a mathematical model to investigate the dynamics of tumor growth between different TANs and responses to various stimuli, and finally to build simulations for brain tumor treatment.

2. Materials & Mathematical Modeling



$$\begin{aligned} \frac{\partial N_1}{\partial t} &= D_{N_1} \Delta N_1 + r_1 N_1 \left(1 - \frac{N_1}{S + K_1}\right) - \alpha_1 N_1 N_2 - \mu_1 N_1 \\ \frac{\partial N_2}{\partial t} &= D_{N_2} \Delta N_2 + r_2 N_2 \left(1 - \frac{N_2}{G + K_2}\right) - \alpha_2 N_2 N_1 - \mu_2 N_2 - \beta N_2 A \\ \frac{\partial A}{\partial t} &= D_A \Delta A + \lambda_A I_A - \mu_A A \\ \frac{\partial S}{\partial t} &= D_S \Delta S + \lambda_S I_S - \mu_S S \\ \frac{\partial G}{\partial t} &= D_G \Delta G + \lambda_G I_G - \mu_G G \\ \frac{\partial n}{\partial t} &= D_n \Delta n + r \left(1 + r_N \frac{N_2^2}{k^2 + N_2^2}\right) n \left(1 - \frac{n}{n_0}\right) - \mu_n N_1 n \end{aligned}$$

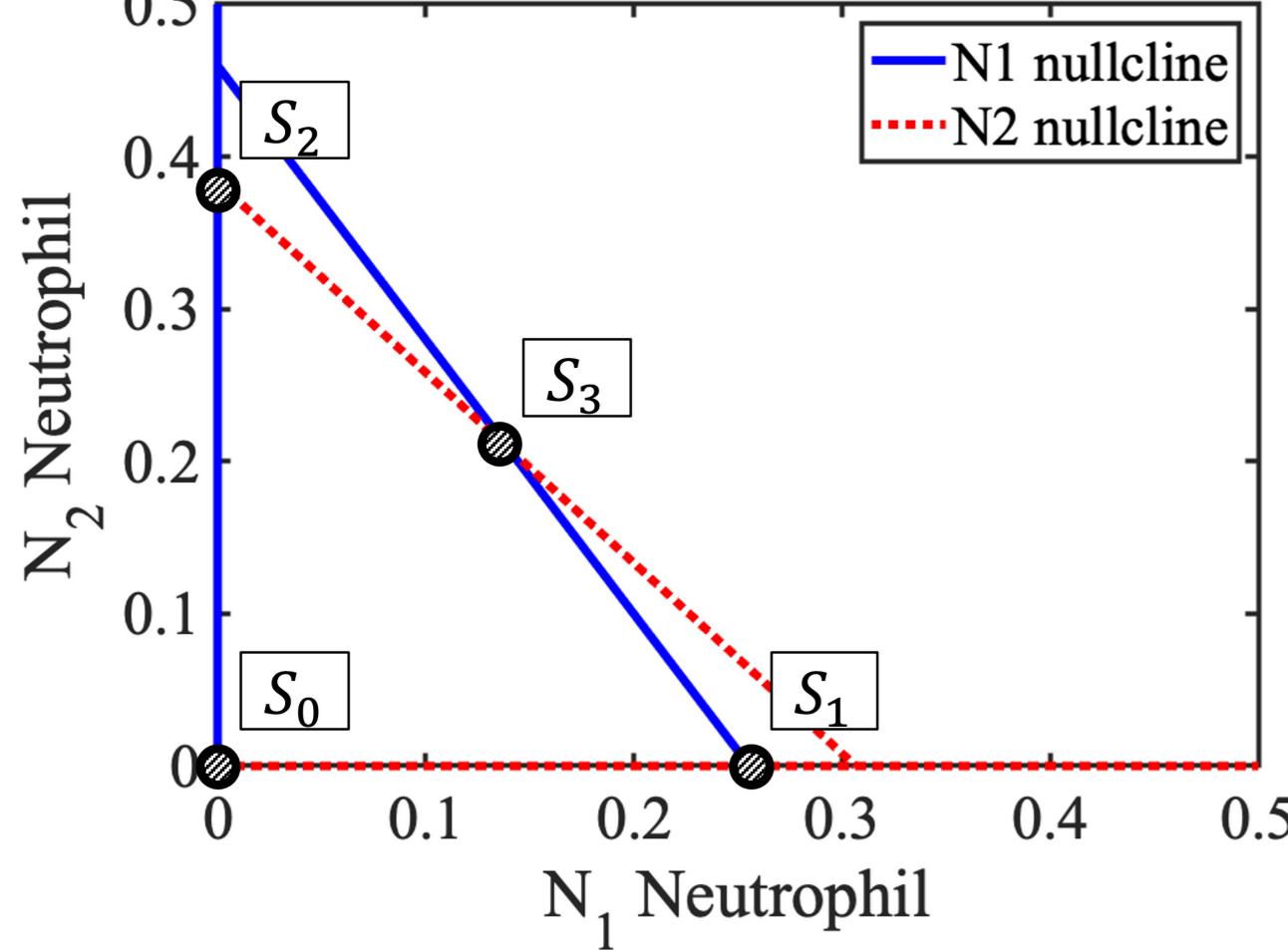
3. ODE Analysis & Results

We can calculate steady states of N_1 , N_2 and analyze their stability analytically.
(※ We assume A , S and G are parameters in this case.)

For every S_i s to be positive, parameters need to satisfy

$$(r_1 - \mu_1) > 0, \quad \text{and whether} \quad \frac{r_1 - \mu_1}{\alpha_1} < \frac{(G + K_2)(r_2 - \mu_2 - \beta A)}{r_2}, \quad \frac{r_2 - \mu_2 - \beta A}{\alpha_2} < \frac{(S + K_1)(r_1 - \mu_1)}{r_1} \quad \dots \text{ (a)}$$

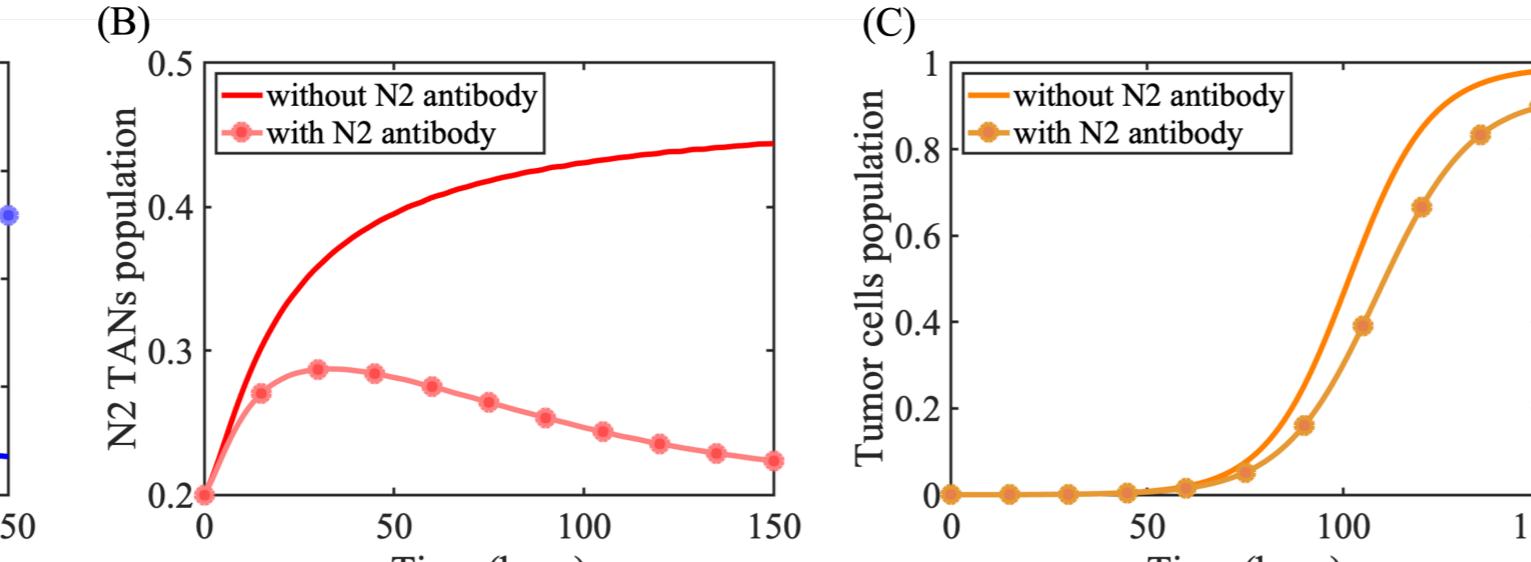
$$(r_2 - \mu_2 - \beta A) > 0 \quad \text{or} \quad \frac{r_1 - \mu_1}{\alpha_1} > \frac{(G + K_2)(r_2 - \mu_2 - \beta A)}{r_2}, \quad \frac{r_2 - \mu_2 - \beta A}{\alpha_2} > \frac{(S + K_1)(r_1 - \mu_1)}{r_1}. \quad \dots \text{ (b)}$$



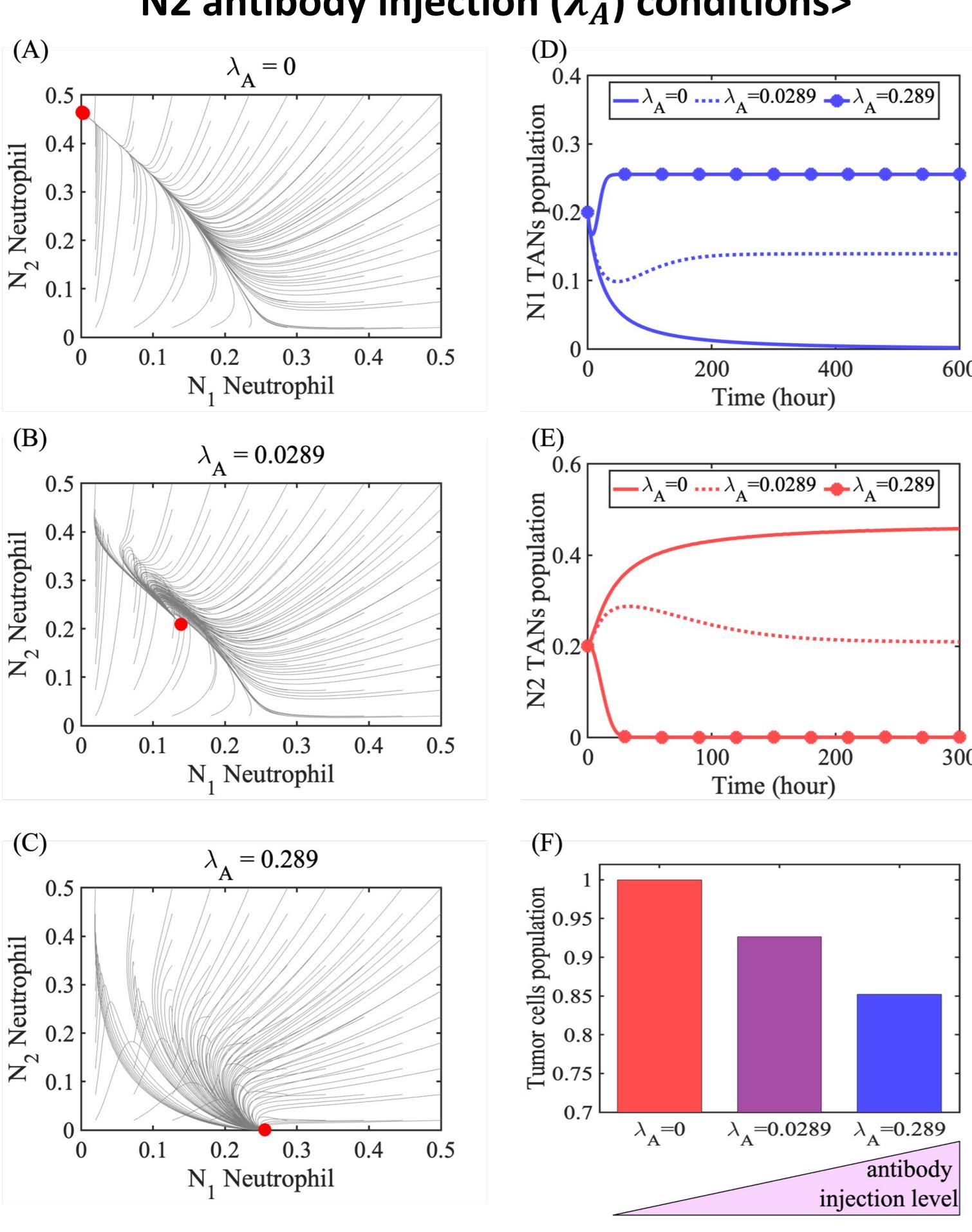
condition	steady state	stability
	when (a) holds	when (b) holds
S_0		unstable
S_1	stable	saddle point
S_2	stable	saddle point
S_3	saddle point	stable

We can examine the dynamics of our model by using numerical solvers.

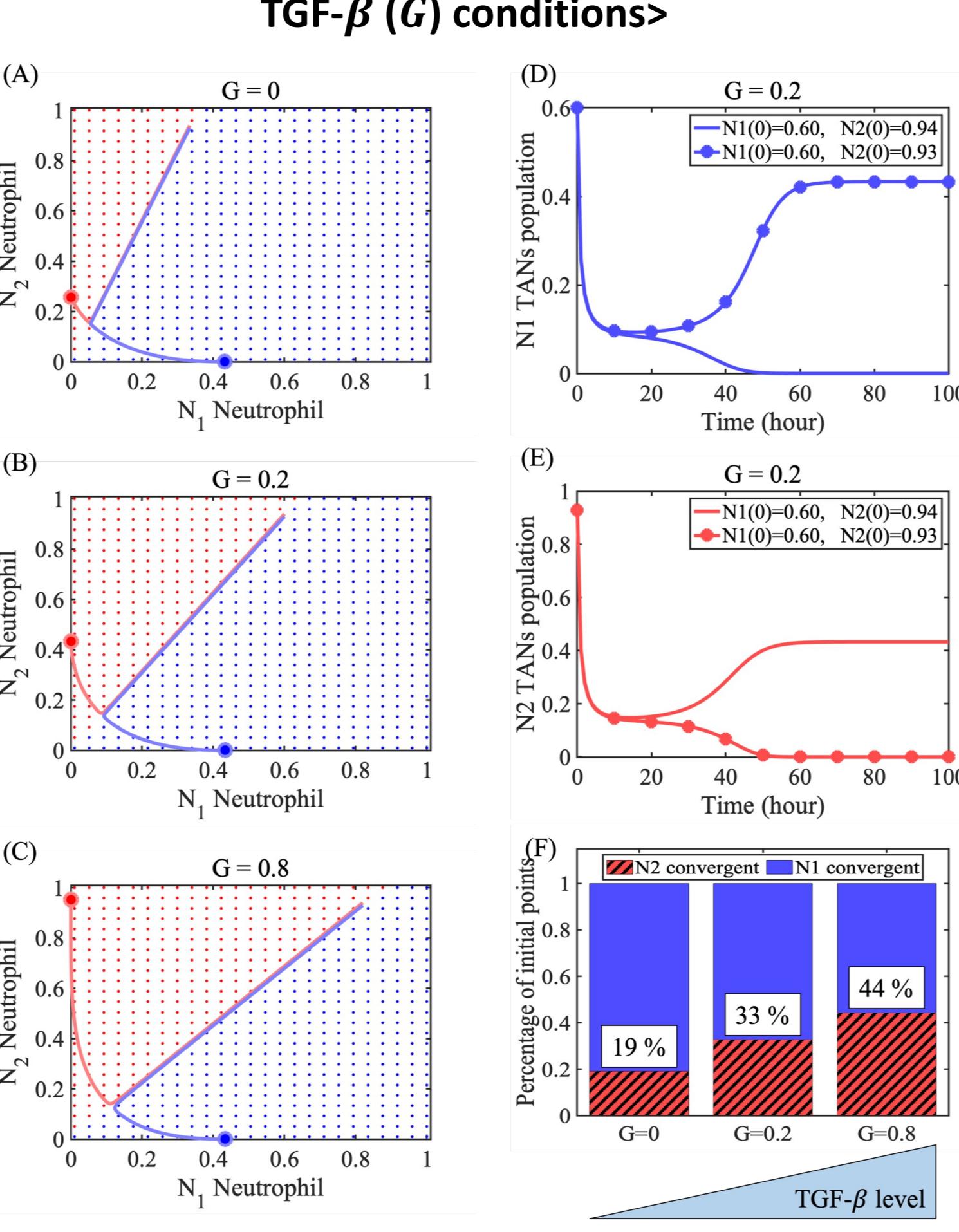
<Basic dynamics according to time evolution with varied N2 antibody injection (λ_A)>



<Dynamics of single stable steady state with various N2 antibody injection (λ_A) conditions>



<Dynamics of bistability state with different TGF-β (G) conditions>



6. References

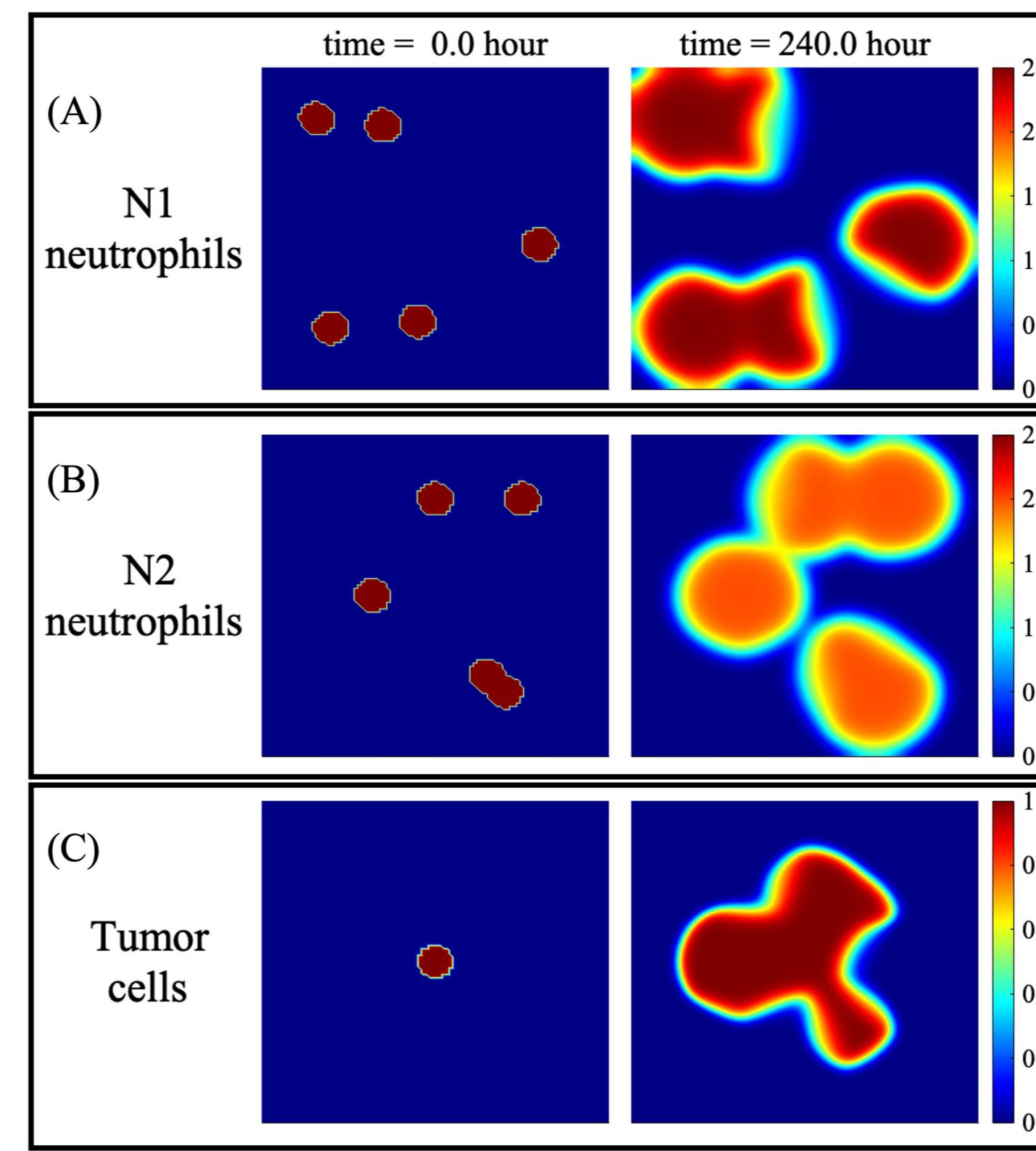
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4. PDE Results

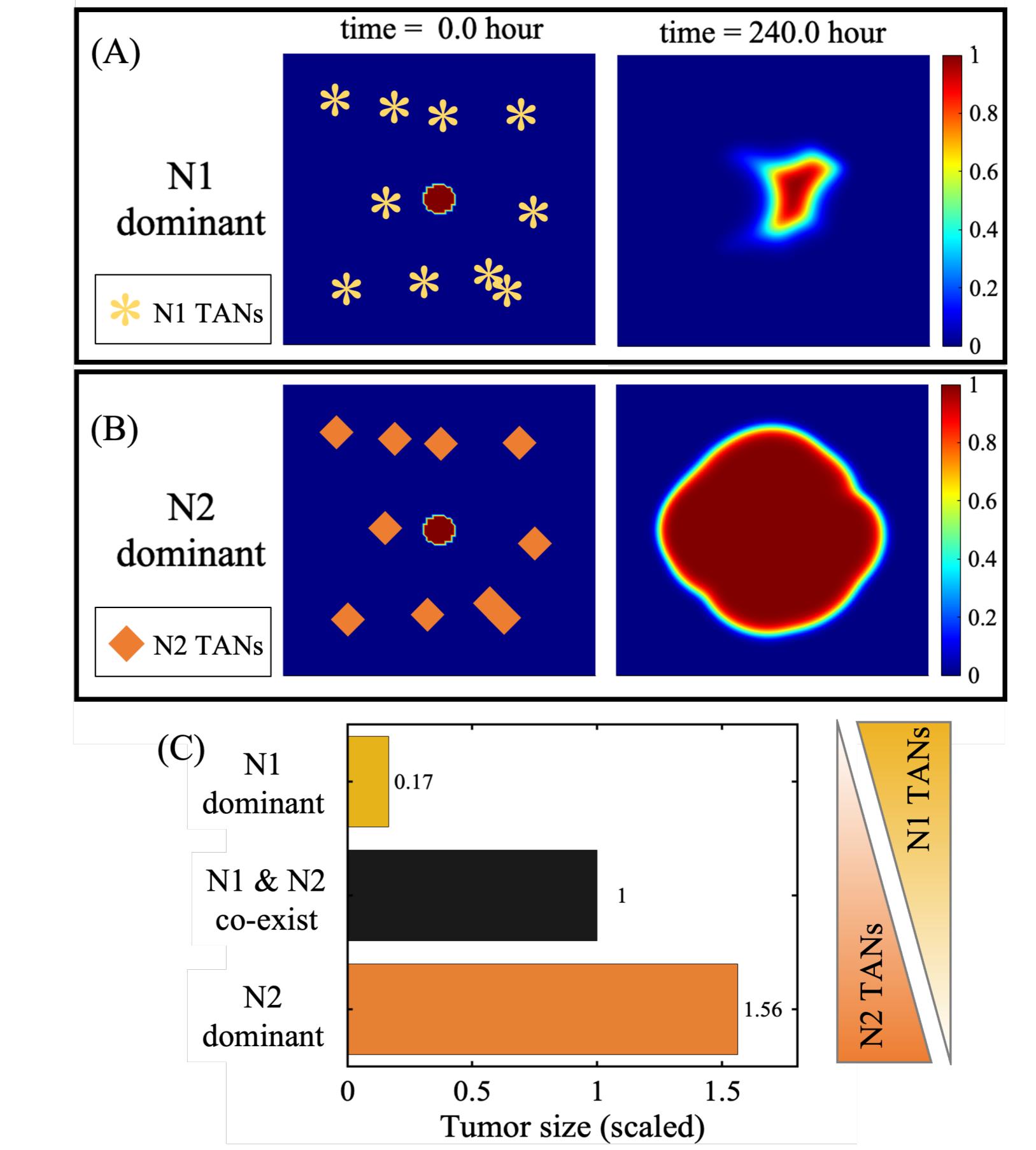
We examine tumor growth with diffusion on 1cm×1cm domain for 240 hours (10 days).

You can see all the PDE results as live animations through QR code URL above.

<Basic diffusion portraits of N1 TANs, N2 TANs and tumor cells>



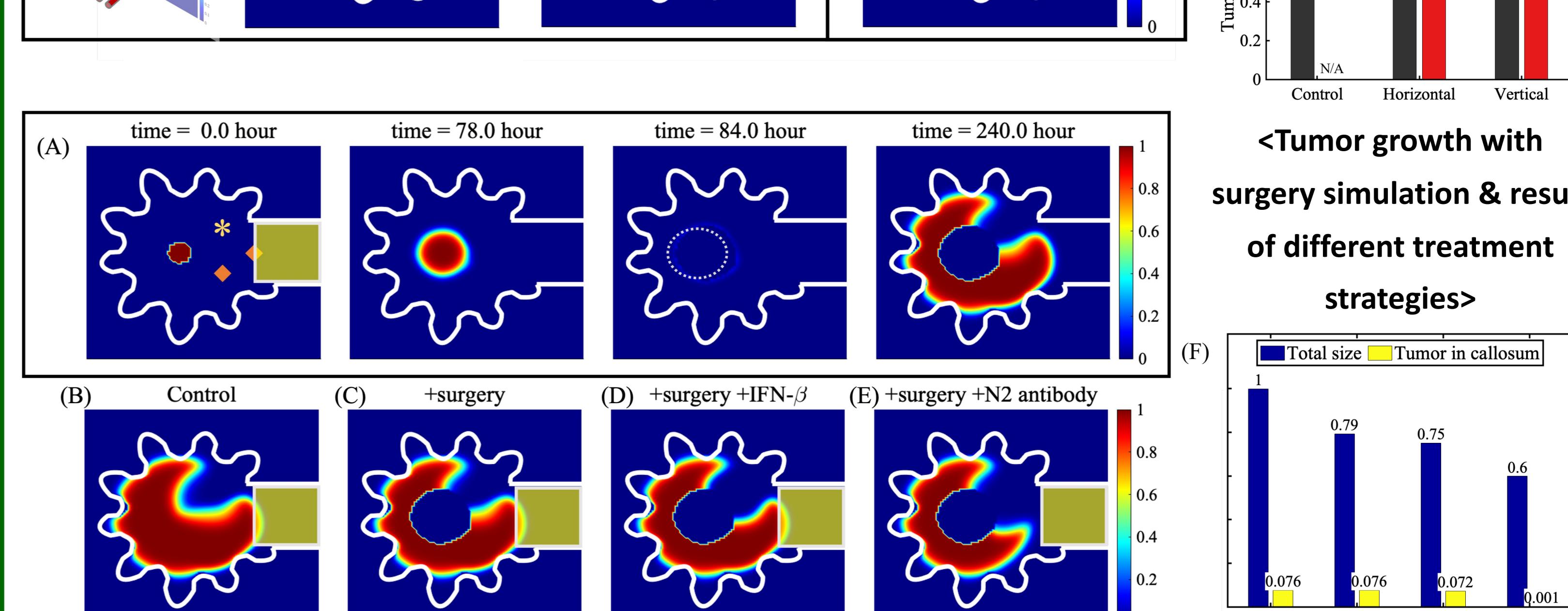
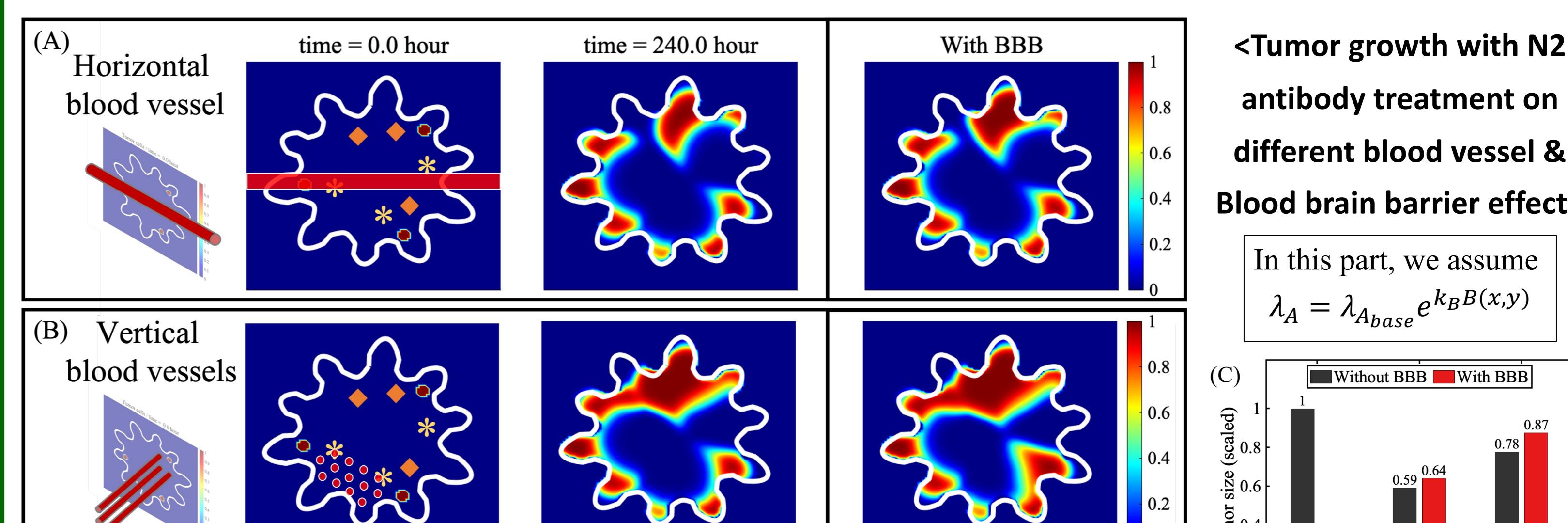
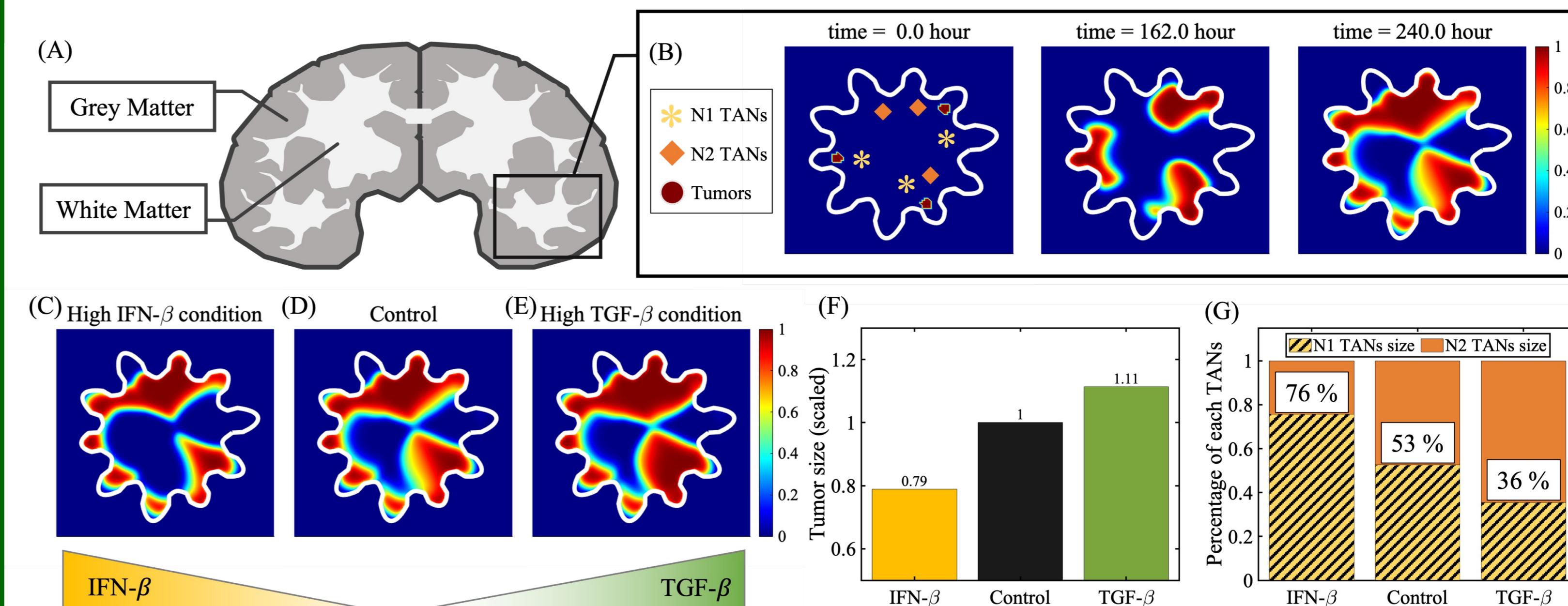
<Tumor growth under different initial conditions and comparison between each cases>



We simulate tumor growth on human brain tissue.

(※ We assume diffusions on grey matter is 10^6 times slow than on white matter.)

<Tumor growth simulation on brain-like domain (top) & results with various chemokine conditions (bottom)>



5. Discussion

- Competition between two different TANs is the key of complex tumor microenvironment, making tumor growth or shrink corresponding to dominant neutrophil type.
- Neutrophil-associated chemokines such as TGF-β and IFN-β affect tumor growth by adjusting neutrophils conditions in tumor microenvironment.
- Treatment for brain tumors can be controlled by reducing N2 TANs condition, with further considerations of brain physiology adds accuracy for treatment simulations.