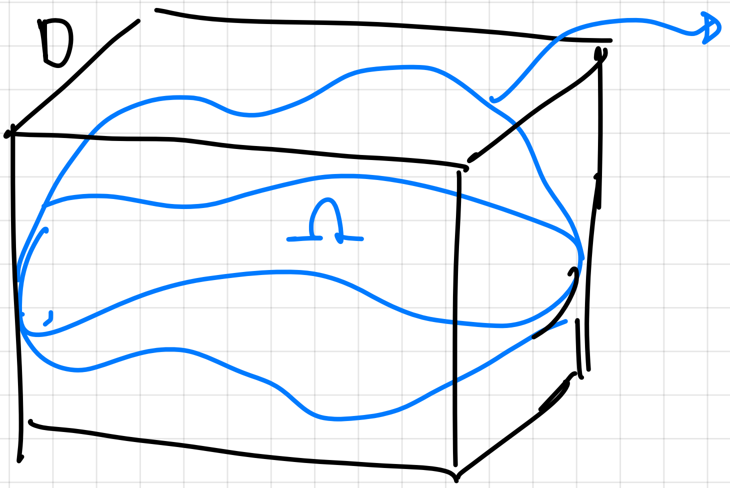
Crecimiento de un tumor - Elementos Finitos

Células tumorales

- $T(\vec{x},t) \equiv$ densidad de células tumorales
- $D_T \equiv$ constante de difusividad del tumor
- $a_T \equiv$ tasa de crecimiento intrínseco de las c. tumorales
- $\alpha_{T,N} \equiv$ tasa de muerte de las células tumorales por competición con células normales

Células normales

- $N(\vec{x},t) \equiv$ densidad de células normales
- $D_N \equiv$ constante de difusividad del tejido normal ($D_N \ll D_T$)
- $a_N \equiv$ tasa de crecimiento intrínseco de c. normales
- $\alpha_{N,T} \equiv$ tasa de muerte de c. normales por competición con c. tumorales



$$T_0(\vec{x}) = \begin{cases} \text{gaussiana} & x \in \Omega \\ 0 & x \notin \Omega \end{cases}$$

$$N_0(\vec{x}) = \begin{cases} 1-\text{gaussiana} & x \in \Omega \\ 1 & x \notin \Omega \end{cases}$$

$$\begin{cases} \dfrac{\partial T}{\partial t} = D_T \Delta T + a_T\left(1-\dfrac{T}{k_T}\right)T - \alpha_{T,N} N T, & \text{en } D\times(0,T) \\[2ex] \dfrac{\partial N}{\partial t} = \underbrace{D_N \Delta N}_{\text{difusión}} + \underbrace{a_N\left(1-\dfrac{N}{k_N}\right)N}_{\text{crecimiento}} - \underbrace{\alpha_{N,T} T N}_{\text{competición}}, & \text{en } D\times(0,T) \end{cases}$$

$$\left.\frac{\partial N}{\partial \vec{n}}\right|_{\partial D} = \left.\frac{\partial T}{\partial \vec{n}}\right|_{\partial D} = 0$$ (no hay flujo saliente del cubo)

Parámetros

Symbol	Parameter	Value
a_C	Reabsorption rate for the drug [39]	11.3 per day
a_N	Intrinsic growth rate for normal tissue	8.64e−7 per day
a_T	Intrinsic growth rate for tumor cells [37]	1.20e−2 per day
D_C	Diffusion coefficient for drug concentration [39]	2.16e−1 cm^2 per day
D_N	Diffusion coefficient for normal tissue	1.0e−15 cm^2 per day
D_T	Diffusion coefficient for tumor cells [37]	4.2e−3 cm^2 per day
k_N	Normal tissue carrying capacity	1.0
k_T	Tumor cell carrying capacity	1.0
q_C	Drug delivery final cost coefficient	0.1
q_T	Tumor burden final cost coefficient	0.1
r_T	Tumor burden running cost coefficient	0.2
s_U	Drug delivery running cost coefficient	0.05
R_T	Initial tumor radius	1.25 cm
R_D	Initial drug radius	1.25 cm
wU_C	Weight of U_0 drug control distributions	8.0
$\alpha_{T,N}$	Death rate of tumor cells due to competition	1.0e−4 per day
$\alpha_{N,T}$	Death rate of normal tissue due to competition	1.0e−4 per day
$\kappa_{T,C}$	Death rate of tumor cells due to treatment	8.0 per day
$\kappa_{N,C}$	Death rate of normal tissue due to treatment	1.0e−4 per day

Discretización

(primero para T, luego para N)

Euler implícito: $\frac{\partial T}{\partial t} = f(T,N) \rightarrow T^{n+1} = T^n + \Delta t\, f(T^{n+1}, N^{n+1})$

$$\begin{cases} T^{n+1} = T^n + \Delta t \left(D_N \Delta T^{n+1} + a_T\left(1 - \frac{T^{n+1}}{k_T}\right) T^{n+1} - \alpha_{T,N} T^{n+1} N^{n+1} \right) \\ \frac{\partial T^{n+1}}{\partial \vec{n}}\Big|_{\partial D} = 0 \end{cases}$$

Despejando T^{n+1}:

$$(1 - \Delta t\, a_T) T^{n+1} + \Delta t\, \alpha_{T,N} N^{n+1} T^{n+1} + \frac{a_T}{k_T} (T^{n+1})^2 - \Delta t\, D_N \Delta T^{n+1} = T^n$$

(Problema elíptico del tipo $au + bu^2 - c\Delta u = f$)
↑ término no lineal

Formulación variacional

Sea $v \in H^1(D)$, encontrar $T^{n+1} \in H^1(D)$ t.q.

$$(1 - \Delta t\, a_T) \int_D T^{n+1} v + \Delta t\, \alpha_{T,N} \int_D T^{n+1} N^{n+1} v^{*} + \frac{a_T}{k_T} \int_D (T^{n+1})^2 v^{**} +$$

$$+ \Delta t\, D_T \int_D \nabla T^{n+1} \nabla v = \int_D T^n v + \Delta t\, D_T \int_{\partial D} \cancelto{0}{\frac{\partial T}{\partial \vec{n}}} v$$

$$\forall v \in H^1(D)$$

(*) Definimos $w_h^{n+1} = \sum_{i=1}^{N} w_i^{n+1} \phi_i$, tal que en cada nodo tenga el mismo valor que $T^{n+1} N^{n+1}$, es decir,

$$w_h^{n+1}(x_i) = w_i^{n+1} = T^{n+1}(x_i) N^{n+1}(x_i), \quad 1 \leq i \leq N.$$

(**) Definimos $z_{T,h}^{n+1} = \sum_{i=1}^{N} z_{T,i}^{n+1} \phi_i$, tal que en cada nodo tenga el mismo valor que $(T^{n+1})^2$, es decir,

$$z_{T,h}^{n+1}(x_i) = z_{T,i}^{n+1} = (T^{n+1}(x_i))^2, \quad 1 \leq i \leq N$$

Pasamos al espacio de elementos finitos $V_h \subset V \subset H^1(D)$

$T_h^{n+1} = \sum T_i^{n+1} \phi_i$; Encontrar $T_h^{n+1} \in V_h$ tq.

$$(1 - \Delta t\, a_T) \int_D T_h^{n+1} v_h + \Delta t \alpha_{T,N} \int_D w_h^{n+1} v_h + \frac{a_T}{K_T} \int_D z_{T,h}^{n+1} v_h + $$
$$+ \Delta t D_T \int_D \nabla T_h^{n+1} \nabla v_h = \int_D T_h^n v_h \qquad \forall v_h \in V_h$$

$1 \leq j \leq N$

$$(1 - \Delta t\, a_T) \sum T_i^{n+1} \int_D \phi_i \phi_j + \Delta t \alpha_{T,N} \sum w_i^{n+1} \int_D \phi_i \phi_j +$$
$$+ \frac{a_T}{k_T} \sum z_{T,i}^{n+1} \int_D \phi_i \phi_j + \Delta t D_T \sum T_i^{n+1} \int_D \nabla \phi_i \nabla \phi_j = \sum T_i^n \int_D \phi_i \phi_j$$

En forma matricial: si $A_T = (1-\Delta t a_T) M + \Delta t D_T R$,

$$A_T \vec{T}^{n+1} + \Delta t \, \alpha_{T,N} M \vec{w}^{n+1} + \frac{a_T}{K_T} M \vec{z}_T^{n+1} = M \vec{T}^n$$

De manera análoga, se puede desarrollar la ecuación para N, obteniendo

$$A_N \vec{N}^{n+1} + \Delta t \, \alpha_{N,T} M \vec{w}^{n+1} + \frac{a_N}{K_N} M \vec{z}_N^{n+1} = M \vec{N}^n$$

donde $A_N = (1-\Delta t a_N) M + \Delta t D_N R$

y $z_{N,h}^{n+1} = \sum z_{N,i}^{n+1} \phi_i$, con $z_{N,i} = (N^{n+1}(x_i))^2$

Obtenemos el sistema no lineal.

$$\begin{cases} A_T \vec{T}^{n+1} + \Delta t \, \alpha_{T,N} M \vec{w}^{n+1} + \frac{a_T}{K_T} M \vec{z}_T^{n+1} = M \vec{T}^n \\ A_N \vec{N}^{n+1} + \Delta t \, \alpha_{N,T} M \vec{w}^{n+1} + \frac{a_N}{K_N} M \vec{z}_N^{n+1} = M \vec{N}^n \\ (\vec{w}^{n+1})_i = (\vec{T}^{n+1})_i (\vec{N}^{n+1})_i \qquad w_i^{n+1} = T_i^{n+1} N_i^{n+1} \\ (\vec{z}_T^{n+1})_i = (\vec{T}^{n+1})_i (\vec{T}^{n+1})_i \\ (\vec{z}_N^{n+1})_i = (\vec{N}^{n+1})_i (\vec{N}^{n+1})_i \end{cases}$$

5 ecuaciones y 5 incógnitas → Newton-Raphson.

(más adelante se implementa Crank-Nicolson)

Para evitar el sistema no lineal y no tener que utilizar Newton-Raphson, debemos utilizar un método explícito (al menos en los términos no lineales), de manera que $T^{n+1}N^{n+1}$, $(T^{n+1})^2$ no sean incógnitas sino que sean T^nN^n, $(T^n)^2$ ya calculados en el instante de tiempo anterior.

→ Euler explícito: $\frac{\partial T}{\partial t} = f \Rightarrow T^{n+1} = T^n + \Delta t\, f^n$

$$\begin{cases} T^{n+1} = T^n + \Delta t\left(D_T \Delta T^n + a_T\left(1-\frac{T^n}{k_T}\right)T^n - \alpha_{T,N} N^n T^n\right) \\ \frac{\partial T^{n+1}}{\partial \vec{n}}\Big|_{\partial D} = 0 \end{cases}$$

→ Formulación variacional: encontrar $T^{n+1} \in H^1(D)$ t.q.

$$\int_D T^{n+1} v = \int_D T^n v - \Delta t D_T \left[\int_D \nabla T^n \nabla v + \cancelto{0}{\int_{\partial D} \frac{\partial T^n}{\partial \vec{n}} v}\right] +$$

$$+ \Delta t a_T \int_D T^n v - \Delta t \frac{a_T}{k_T} \int_D (T^n)^2 v - \alpha_{T,N} \Delta t \int_D N^n T^n v; \quad \forall v \in H^1(D)$$

Definimos $w_h^n = \sum_{i=1}^{N} w_i^n \phi_i$ tq. $w_h^n(x_i) = w_i^n = N^n(x_i)\, T^n(x_i)$

$z_{T,h}^n = \sum_{i=1}^{N} z_{T,i}^N \phi_i$ tq. $z_{T,h}^n(x_i) = z_{T,i}^n = (T^n(x_i))^2$

$z_{N,h}^n = \sum z_{N,i}^n \phi_i$ tq. $z_{N,h}^n(x_i) = z_{N,i}^n = (N^n(x_i))^2$

Pasamos al espacio de elementos finitos $V_h \subset V \subset H^1(D)$

Encontrar $T^{n+1} \in V_h$ t.q.

$$\sum_{i=1}^{N} T_i^{n+1} \int_D \phi_i \phi_j = (1+\Delta t a_T) \sum_{i=1}^{N} T_i^n \int_D \phi_i \phi_j - \Delta t D_T \sum_{i=1}^{N} T_i^n \int_D \nabla\phi_i \nabla\phi_j -$$

$$- \Delta t \frac{a_T}{k_T} \sum_{i=1}^{N} z_{T,i}^n \int_D \phi_i \phi_j - \Delta t \alpha_{T,N} \sum_{i=1}^{N} \omega_i^n \int_D \phi_i \phi_j \quad 1 \leq j \leq N$$

En forma matricial,

$$M \vec{T}^{n+1} = \left[(1+\Delta t a_T) M - \Delta t D_T R \right] \vec{T}^n - \Delta t \frac{a_T}{k_t} M \vec{z}_T^{\,n} - \Delta t \alpha_{T,N} M \vec{\omega}^n$$

$$M \vec{N}^{n+1} = \left[(1+\Delta t a_N) M - \Delta t D_N R \right] \vec{N}^n - \Delta t \frac{a_N}{k_N} M \vec{z}_N^{\,n} - \Delta t \alpha_{N,T} M \vec{\omega}^n$$

donde $(\vec{z}_T^{\,n})_i$ no es más que $(\vec{T}^n)_i (\vec{T}^n)_i$,

$$(\vec{z}_N^{\,n})_i = (\vec{N}^n)_i (\vec{N}^n)_i \quad ; \quad (\vec{\omega})_i = (\vec{T}^n)_i (\vec{N}_i^n)$$

Intentémoslo con un método explícito de orden 2:

Método de Euler mejorado: $y^{n+1} = y^n + \Delta t\, f\left(t_n + \frac{\Delta t}{2}, y^n + \frac{\Delta t}{2} \underbrace{f(t_n, y^n)}_{k_1}\right)$

$$k_2 = f\left(t_n + \frac{\Delta t}{2}, y^n + \frac{\Delta t}{2} k_1\right)$$

$$K_T^n = T^n + \frac{\Delta t}{2}\left[D_T \Delta T^n + a_T\left(1 - \frac{T^n}{k_T}\right) T^n - \alpha_{T,N} N^n T^n\right]$$

$$K_N^n = N^n + \frac{\Delta t}{2}\left[D_N \Delta N^n + a_N\left(1 - \frac{N^n}{k_N}\right) N^n - \alpha_{N,T} T^n N^n\right]$$

$$T^{n+1} = T^n + \Delta t\left[D_T \Delta K_T^n + a_T\left(1 - \frac{K_T^n}{k_T^n}\right) K_T^n - \alpha_{T,N} K_N^n K_T^n\right]$$

$$N^{n+1} = N^n + \Delta t\left[D_N \Delta K_N^n + a_N\left(1 - \frac{K_N^n}{k_N^n}\right) K_N^n - \alpha_{N,T} K_T^n K_N^n\right]$$

La formulación variacional y la forma matricial las he implementado directamente en MATLAB. Queda:

$$M \vec{K}_T^n = \left((1 + \Delta t a_T) M - \Delta t D_T R\right) \vec{T}^n - \frac{\Delta t a_T}{k_T} M \vec{z}_T^n - \Delta t \alpha_{T,N} M \vec{w}^n$$

(idem para $\vec{K}_N^n$)

luego $(w^n)_i = (K_T^n)_i (K_N^n)_i$; $(z_T^n)_i = (K_T^n)_i^2$; $(z_N^n)_i = (K_N^n)_i^2$

y finalmente

$$M \vec{T}^{n+1} = \left((1 + \Delta t a_T) M - \Delta t D_T R\right) \vec{K}_T^n - \frac{\Delta t a_T}{k_T} \vec{z}_T^n - \Delta t \alpha_{T,N} M \vec{w}^n$$

(idem para $\vec{N}^{n+1}$)

Ahora probamos a resolver con Euler explícito, pero sustituyendo el término ΔT^n por una aproximación de orden 2: $\Delta T^n \simeq \frac{1}{2}(\Delta T^{n+1} + \Delta T^{n-1})$, obteniendo un esquema implícito en el término del Laplaciano.

$$T^{n+1} = T^n + \Delta t \left(\frac{D_T}{2} (\Delta T^{n+1} + \Delta T^{n-1}) + a_T \left(1 - \frac{T^n}{K_T}\right) T^n - \alpha_{T,N} N^n T^n \right)$$

$$\left(M + \frac{\Delta t D_T}{2} R\right) \vec{T}^{n+1} = M \left[(1 + a_T \Delta t) \vec{T}^n - \frac{a_T \Delta t}{K_T} \vec{z}_T^{\,n} - \Delta t \alpha_{T,N} \vec{W}^n \right] - \frac{\Delta t D_T}{2} R \vec{T}^{n-1}$$

Por tanto, ya tenemos 3 maneras diferentes de resolverlo. Nos proponemos otros objetivos:

- Implementar Crank-Nicolson resolviendo con Newton-Raphson, debido a los términos no lineales
- Resolver el problema en 3 dimensiones.

CRANK-NICOLSON.

Discretizacion:

$$T^{n+1} = T^n + \frac{\Delta t}{2}\Big[D_T\left(\Delta T^{n+1} + \Delta T^n\right) + a_T\left(T^{n+1} + T^n\right) - \frac{a_T}{k_T}\left((T^{n+1})^2 + (T^n)^2\right) - \alpha_{T,N}\left(N^{n+1}T^{n+1} + N^n T^n\right)\Big]$$

Reordenando,

$$\left(1 - \frac{\Delta t\, a_T}{2}\right) T^{n+1} - \frac{\Delta t\, D_T}{2}\Delta T^{n+1} + \frac{\Delta t\, a_T}{2k_T}\overbrace{(T^{n+1})^2}^{z_T^{n+1}} + \frac{\Delta t}{2}\alpha_{T,N}\overbrace{N^{n+1}T^{n+1}}^{w^{n+1}} =$$

$$= \left(1 + \frac{\Delta t\, a_T}{2}\right) T^n + \frac{\Delta t\, D_T}{2}\Delta T^n - \frac{\Delta t\, a_T}{2k_T}\underbrace{(T^n)^2}_{z_T^n} - \frac{\Delta t\, \alpha_{T,N}}{2}\underbrace{N^n T^n}_{w^n}$$

(Sistema de EDOs no lineal)

Formulacion variacional + forma matricial:

$$\begin{cases} M\cdot\left[\left(1 - \frac{\Delta t\, a_T}{2}\right)\vec{T}^{n+1} + \frac{\Delta t\, a_T}{2k_T}\vec{z}_T^{\,n+1} + \frac{\Delta t}{2}\alpha_{T,N}\vec{w}^{\,n+1}\right] + \frac{\Delta t\, D_T}{2} R\,\vec{T}^{n+1} = \\ = M\left[\left(1 + \frac{\Delta t\, a_T}{2}\right)\vec{T}^n - \frac{\Delta t\, a_T}{2k_T}\vec{z}_T^{\,n} - \frac{\Delta t\, \alpha_{T,N}}{2}\vec{w}^{\,n}\right] - \frac{\Delta t\, D_T}{2} R\,\vec{T}^n \\ M\cdot\left[\left(1 - \frac{\Delta t\, a_N}{2}\right)\vec{N}^{n+1} + \frac{\Delta t\, a_N}{2k}\vec{z}_N^{\,n+1} + \frac{\Delta t}{2}\alpha_{N,T}\vec{w}^{\,n+1}\right] + \frac{\Delta t\, D_N}{2} R\,\vec{N}^{n+1} = \\ = M\left[\left(1 + \frac{\Delta t\, a_N}{2}\right)\vec{N}^n - \frac{\Delta t\, a_N}{2k}\vec{z}_N^{\,n} - \frac{\Delta t\, \alpha_{N,T}}{2}\vec{w}^{\,n}\right] - \frac{\Delta t\, D_N}{2} R\,\vec{N}^n \\ (z_N^{n+1})_i = (N^{n+1})_i^2; \quad (z_T^{n+1})_i = (T^{n+1})_i^2 \quad ; \; (w^{n+1})_i = (T^{n+1})_j\,(N^{n+1})_i \end{cases}$$

Obtenemos un sistema algebraico no lineal de $5 \cdot N$ ecuaciones y $5 \cdot N$ incognitas, siendo $N \equiv$ nº de nodos.

Resolveremos con Newton-Raphson: como las ecs. son de la forma

$$f\left(\vec{T}^{n+1}, \vec{N}^{n+1}, \vec{z}_T^{\,n+1}, \vec{z}_N^{\,n+1}, \vec{w}^{n+1}\right) = 0,$$

calculamos la Jacobiana: $JF =$

$$= \left[\begin{array}{c|c|c|c|c}
\left(1 - \frac{a_T \Delta t}{2}\right) M + \frac{\Delta t D_T}{2} R & 0 & \frac{\Delta t\, a_T}{2 K_T} M & 0 & \frac{\Delta t\, \alpha}{2} M \\
0 & \left(1 - \frac{a_N \Delta t}{2}\right) M + \frac{\Delta t D_N}{2} R & 0 & \frac{\Delta t\, a_N}{2 K_N} M & \frac{\Delta t\, \alpha}{2} M \\
-2\vec{T}^{n+1}\;{}^{*} & 0 & I & 0 & 0 \\
0 & -2\vec{N}^{n+1}\;{}^{*} & 0 & I & 0 \\
-\vec{N}^{n+1}\;{}^{*} & -\vec{T}^{n+1}\;{}^{*} & 0 & 0 & I
\end{array}\right]$$

Para cada instante de tiempo, haremos $X^{n+1} = X^n - JF^{-1}(X^n)\, F(X^n)$

donde X^n representa el vector $\left(\vec{T}^n; \vec{N}^n; \vec{z}_T^{\,n}; \vec{z}_N^{\,n}; \vec{w}^n\right)$

* matriz diagonal con los valores del vector.