Reduced Model For 2D Tumor Growth

Drug-Free dynamic

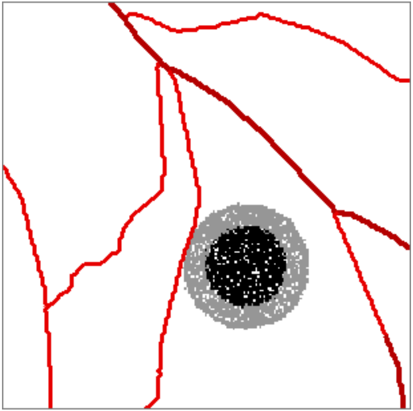
Mazen Alamir & Mirko Fiacchini

CNRS, University of Grenoble

Outline

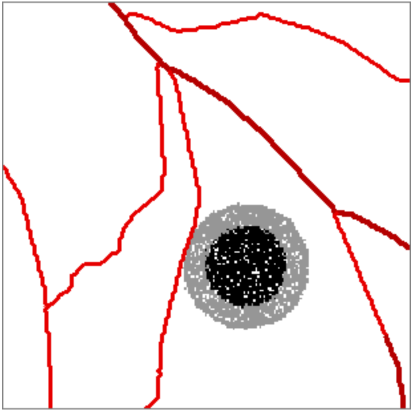
1. Available Data
2. Model Derivation
3. Identification
4. Validation Results

Available Data



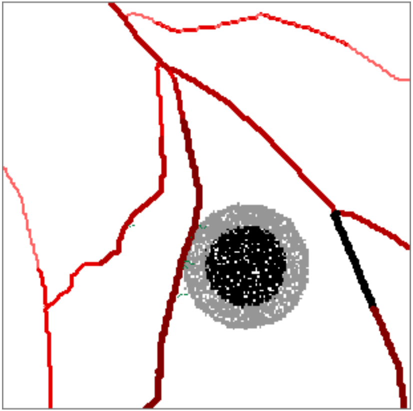
t=1 day

Available Data



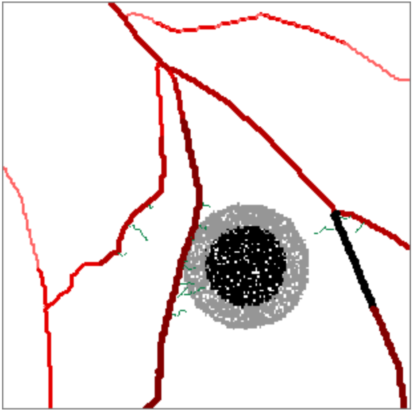
t=2 days

Available Data



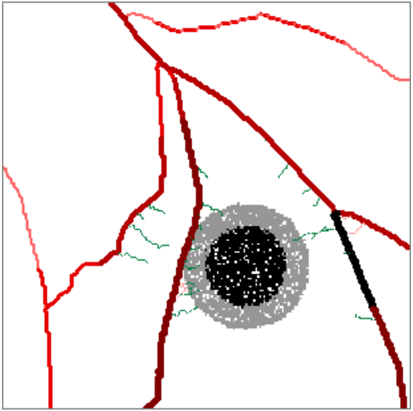
t=3 days

Available Data



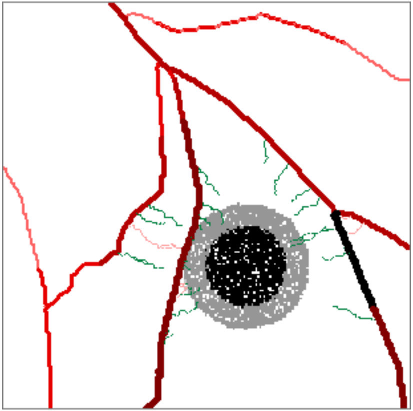
t=4 days

Available Data



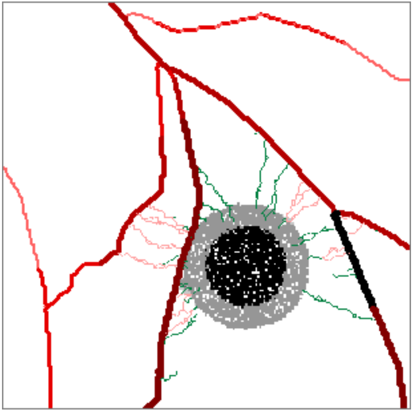
t=5 days

Available Data



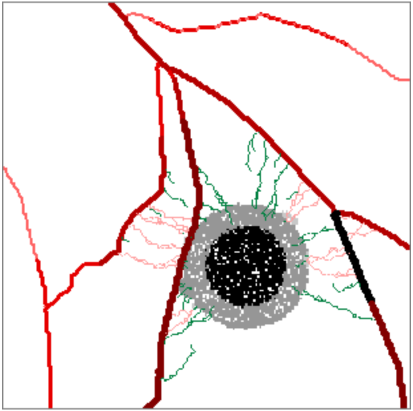
t=6 days

Available Data



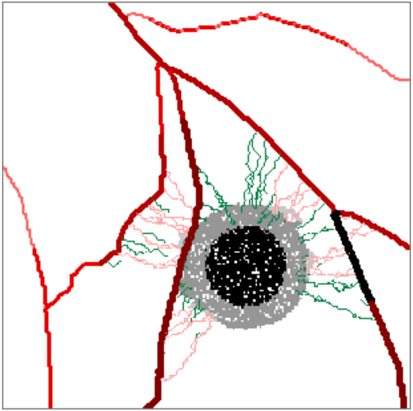
t=8 days

Available Data



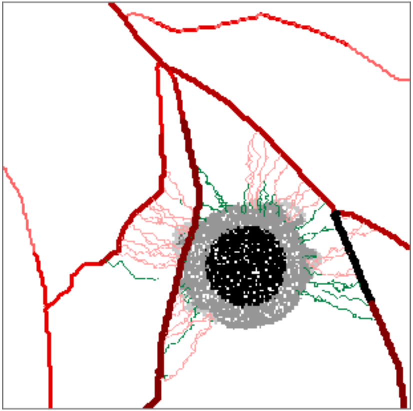
t=10 days

Available Data



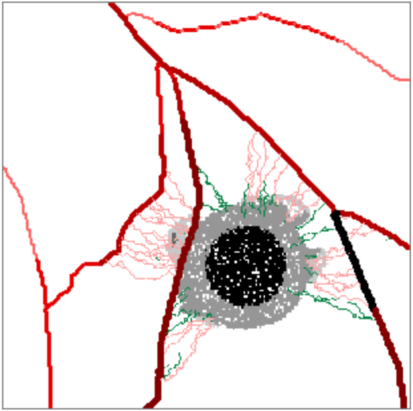
t=12 days

Available Data



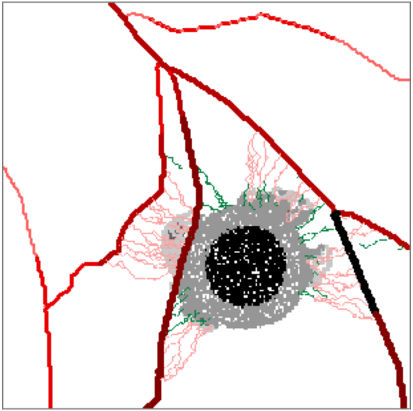
t=14 days

Available Data



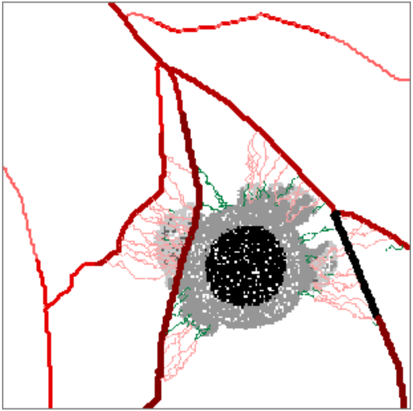
t=16 days

Available Data



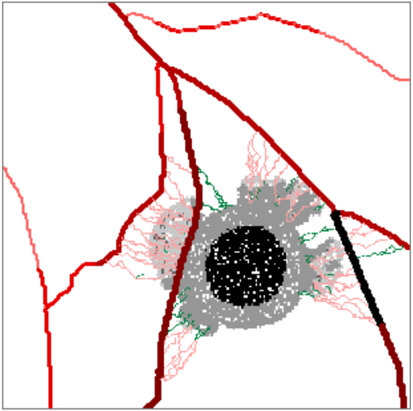
t=18 days

Available Data



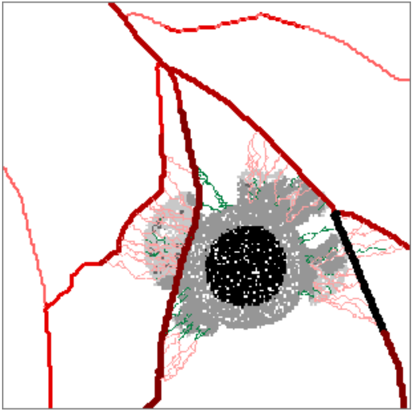
t=20 days

Available Data



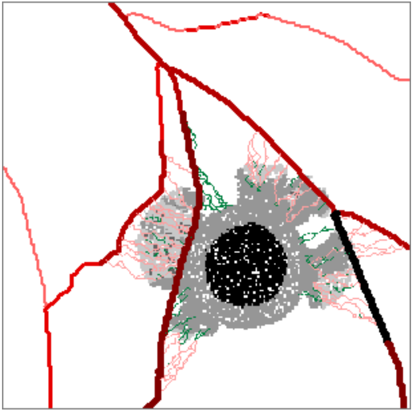
t=22 days

Available Data



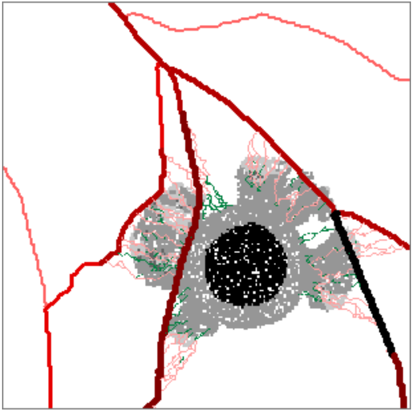
t=24 days

Available Data



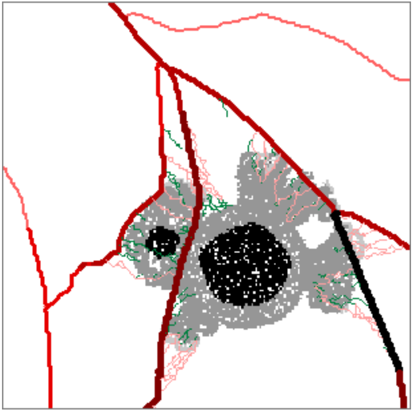
t=26 days

Available Data



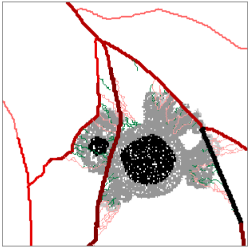
t=28 days

Available Data



t=30 days

Available Data



- 18 colored (rgb) matrices labelled in time
- **Vessels** are represented by:
  Pink, lighred, darkred, verydarkred and green
- **Tumor cells** are represented by:
  black, gray, lightgray and darkgray

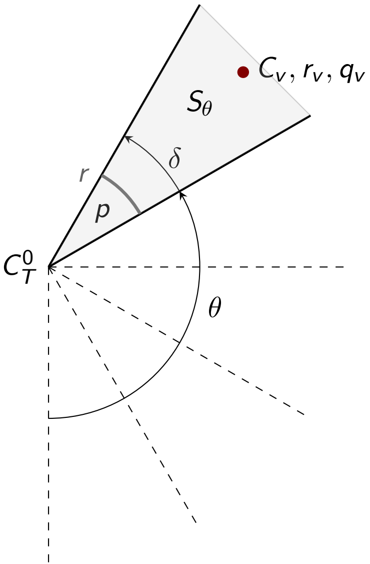
The images are produced by the TIMC simulator under no drug injection.

Objective

Derive a dynamic model that

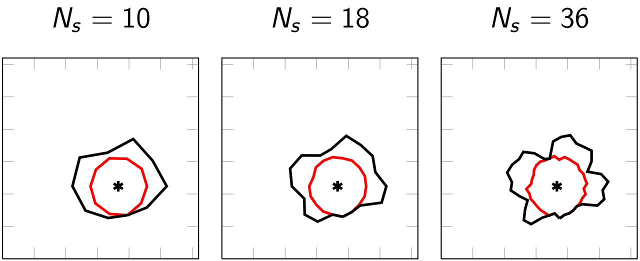
1. depends on the 2D disposition of the vessels/tumor cells
2. is based on physiologically interpretable facts/conjectures
3. is computationally efficient for:
   - Extensive simulations
   - On-line optimization of therapeutical strategies
4. involves few number of easily identifiable parameters.

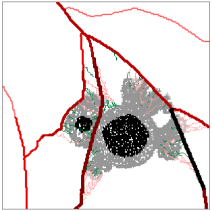
Notation



- C_T^0 initial center of the tumor
- S_θ angular sector
- N_s number of sectors ($\delta := \frac{2\pi}{N_s}$)
- C_v center of the vessels in S_θ
- q_v number of vessels in S_θ
- q number of vessels at tumor
- $\delta_r := \|C_T^0 - C_v\|$
- p number of tumor cells in S_θ
- $r = \sqrt{2p/\delta}$ tumor radius in S_θ

Initial and final radius for different $N_s \in \{5, 9, 18\}$





The positions are defined by

$$\left\{\theta_i, r_i\right\}_{i=1}^{N_s} = \left\{(i\delta, \sqrt{2p_i/\delta})\right\}_{i=1}^{N_s}$$

Key Processes

Two key processes that need to be modeled:

Tumor Growth

How a tumor of size p grows in the presence of q neighboring vessels.

$$\dot{p} = G(p, q)?$$

(Same law for all sectors)

Vessels recruitment

Given initial vessels disposition (q_v^0, δ_r^0), how the tumor p recruits:

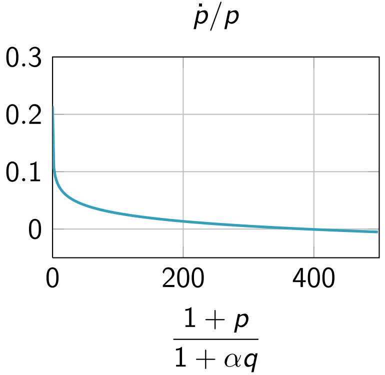
$$\dot{q} = R(p, q, \mathit{disposition})$$

(Same law for all sectors)

The Growth Process

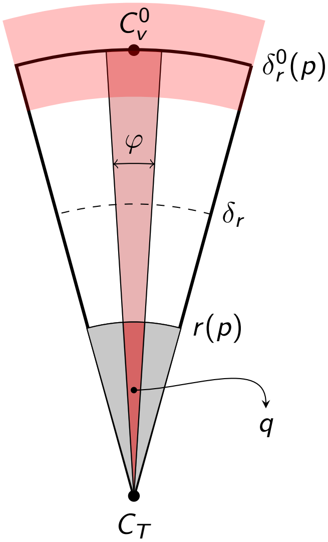
Use a rather *standard* model:

$$\dot{p} = p\Big[\lambda_1 - \lambda_2 \ln(\frac{1+p}{1+\alpha q})\Big] \quad (1)$$



- No growth from $p = 0$
- $(q = 0) \Rightarrow (\dot{p} < 0)$ (death)
- (high q) $\Rightarrow \dot{p} > 0$ (growth)
- α *tunes* the threshold

The Recruitment Process



- Recruitment $\leftrightarrow$ increasing φ
- **Neighboring vessels** (involved in the growth model):

$$q := \frac{1}{2}\big[r(p)\big]^2 \times \varphi$$

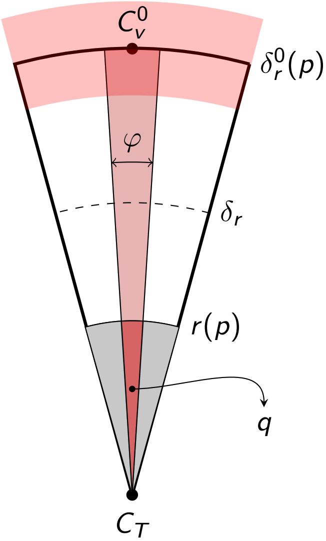
- **Total recruited vessels**:

$$q_{rec} = \frac{1}{2}\left[\delta_r^0\right]^2 \times \varphi = \frac{1}{2}\left[\frac{\delta_r^0}{r(p)}\right]^2 q$$

Position of the c.o.m of vessels:

$$\delta_r \quad = \quad \frac{(q_v^0 - q_{rec}) \times \delta_r^0 + q_{rec} \times \frac{2}{3}\delta_r^0}{q_v^0}$$

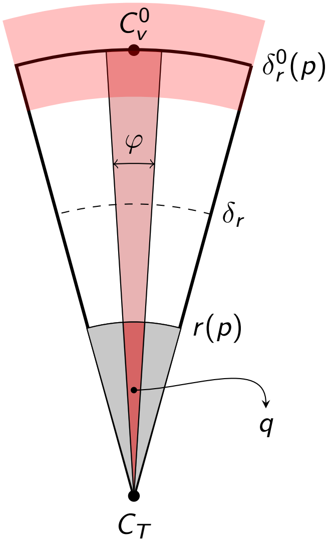
The Recruitment Process



After straightforward manipulation:

$$q := 6\left[1 - \frac{\delta_r}{\delta_r^0}\right]\left[\frac{r(p)}{\delta_r^0}\right]^2 \times q_v^0$$

The Recruitment Process



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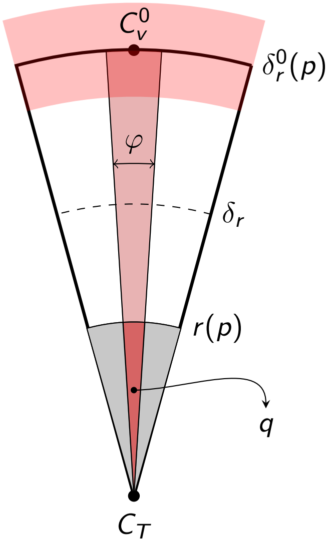
→ q and δ_r are exchangeable.

→ (p, δ_r) : state of a given sector S_θ

The Recruitment Process



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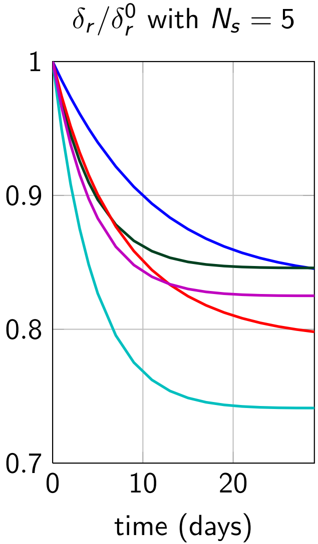
→ (p, δ_r) : state of a given sector S_θ

Road map

look at the data for inspiration . . . !

The Data Regarding δ_r



Data-inspired model:

$$\dot{\delta}_r = \frac{\lambda_r p}{\delta_r}\left[\gamma_r \delta_r^0 - \delta_r\right]$$

Properties: Recruitment is

- faster with p
- slower with distance
- saturated by $\gamma_r \in [0, 1]$
  [physiological/extensibility limit]

Dynamic Model

For any angular sector S_θ:

$$\dot{p} = p\left[\lambda_1 - \lambda_2 \ln\left(\frac{1+p}{1+\alpha q}\right)\right]$$

$$\dot{\delta}_r = \frac{\lambda_r p}{\delta_r}\left[\gamma_r \delta_r^0 - \delta_r\right]$$

- $r(p) := \sqrt{N_s p/\pi}$
- $q := 6\left[1 - \frac{\delta_r}{\delta_r^0}\right]\left[\frac{r(p)}{\delta_r^0}\right]^2 \times q_v^0$
- $(\lambda_1, \lambda_2, \alpha, \lambda_r, \gamma_r) \in \mathbb{R}^5$ are the model parameters. [Identical for all sectors S_θ]

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Problem. Recruitment delay is not represented.

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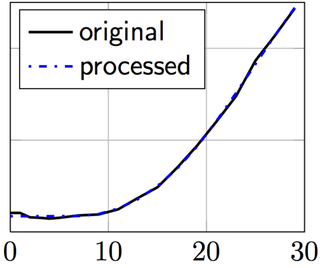

typical evolution of tumor

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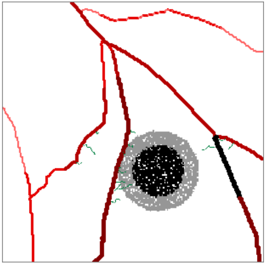

Dynamic Model

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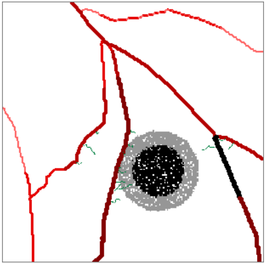
$$\dot{p} = p\Big[\lambda_1 - \lambda_2 \ln\big(\frac{1+p}{1+\alpha q}\big)\Big]$$

$$\dot{\delta}_r = \frac{\lambda_r p}{\delta_r}\Big[\gamma_r \delta_r^0 - \delta_r\Big]$$

- $r(p) := \sqrt{N_s p/\pi}$
- $q_\infty := 6\Big[1 - \frac{\delta_r}{\delta_r^0}\Big]\Big[\frac{r(p)}{\delta_r^0}\Big]^2 \times q_v^0$
- $(\lambda_1, \lambda_2, \alpha, \lambda_r, \gamma_r) \in \mathbb{R}^5$ are the model 1.0 parameters. [Identical for all sectors S_θ]

Problem. Recruitment delay is not represented.



Dynamic Model

For any angular sector S_θ:

$$\dot{p} = p\Big[\lambda_1 - \lambda_2 \ln(\frac{1+p}{1+\alpha q})\Big]$$

$$\dot{\delta}_r = \frac{\lambda_r p}{\delta_r}\Big[\gamma_r \delta_r^0 - \delta_r\Big]$$

$$q = [\mathcal{F}(s)] * q_\infty$$

- $r(p) := \sqrt{N_s p/\pi}$
- $q_\infty := 6\left[1 - \frac{\delta_r}{\delta_r^0}\right]\left[\frac{r(p)}{\delta_r^0}\right]^2 \times q_v^0$
- $(\lambda_1, \lambda_2, \alpha, \lambda_r, \gamma_r) \in \mathbb{R}^5$ are the model 1.0 parameters. [Identical for all sectors S_θ]

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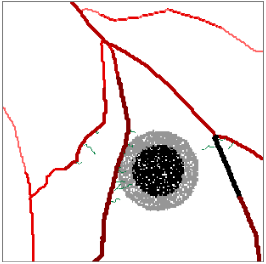


$$\mathcal{F}(s) := \left[\frac{1}{1+\tau s}\right]^{n_q}$$

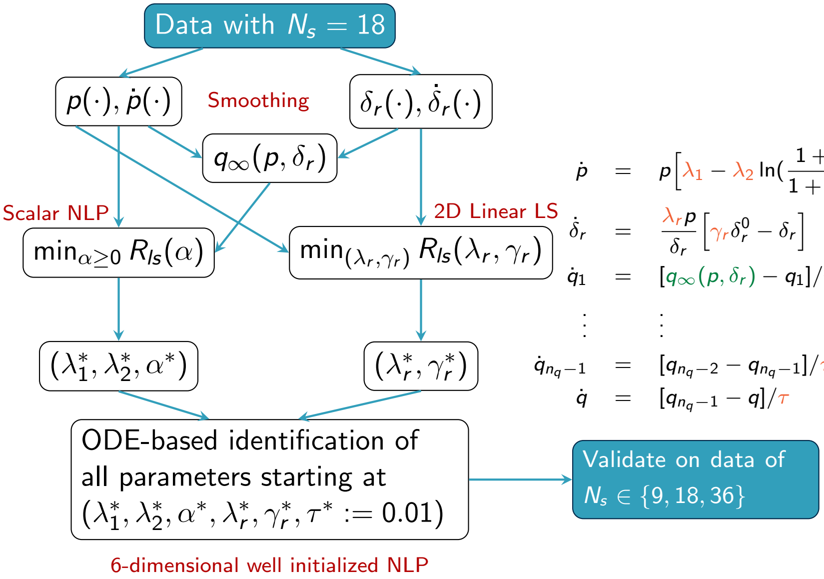
Dynamic Model (Continued)

For any angular sector S_θ:

$$\begin{aligned}
\dot{p} &= p\Big[\lambda_1 - \lambda_2 \ln(\frac{1+p}{1+\alpha q})\Big] \\
\dot{\delta}_r &= \frac{\lambda_r p}{\delta_r}\Big[\gamma_r \delta_r^0 - \delta_r\Big] \\
\dot{q}_1 &= [q_\infty(p,\delta_r) - q_1]/\tau \\
\vdots &\quad \vdots \\
\dot{q}_{n_q-1} &= [q_{n_q-2} - q_{n_q-1}]/\tau \\
\dot{q} &= [q_{n_q-1} - q]/\tau
\end{aligned}$$

- $q_\infty := 6\left[1 - \frac{\delta_r}{\delta_r^0}\right]\left[\frac{r(p)}{\delta_r^0}\right]^2 \times q_v^0$
- $(\lambda_1, \lambda_2, \alpha, \lambda_r, \gamma_r, \tau, n_q) \in \mathbb{R}^6 \times \mathbb{N}$ are the model parameters. [Identical for all sectors S_θ]
- For each sector, a state vector of dimension $n_q + 2$.
- Model dimension $N_s(n_q + 2)$.
- Total number of parameters : 6
- $n_q = 5$ shows appropriate.

Identification



$$
\begin{aligned}
\dot{p} &= p\Big[\lambda_1 - \lambda_2 \ln\Big(\frac{1+p}{1+\alpha q}\Big)\Big] \\
\dot{\delta}_r &= \frac{\lambda_r p}{\delta_r}\Big[\gamma_r \delta_r^0 - \delta_r\Big] \\
\dot{q}_1 &= [q_\infty(p, \delta_r) - q_1]/\tau \\
\vdots \quad & \quad \vdots \\
\dot{q}_{n_q - 1} &= [q_{n_q - 2} - q_{n_q - 1}]/\tau \\
\dot{q} &= [q_{n_q - 1} - q]/\tau
\end{aligned}
$$

Identification Results

$$
\begin{aligned}
\dot{p} &= p\left[\lambda_1 - \lambda_2 \ln\left(\frac{1+p}{1+\alpha q}\right)\right] \\
\dot{\delta}_r &= \frac{\lambda_r p}{\delta_r}\left[\gamma_r \delta_r^0 - \delta_r\right] \\
\dot{q}_1 &= [q_\infty(p,\delta_r) - q_1]/\tau \\
\vdots & \quad \vdots \\
\dot{q}_{n_q-1} &= [q_{n_q-2} - q_{n_q-1}]/\tau \\
\dot{q} &= [q_{n_q-1} - q]/\tau
\end{aligned}
$$

$$
\begin{aligned}
\lambda_1 &= 0.12 \\
\lambda_2 &= 0.02 \\
\alpha &= 0.64 \\
\lambda_r &= 0.009 \\
\gamma_r &= 0.78 \\
\tau &= 1.86 \\
n_q &= 5
\end{aligned}
$$

Validation Protocol

In the absence of new data:

- Identify using $N_s = 18$
- For $N_s \in \{9, 18, 36\}$,
  1. Observe the final tumor form in the (x, y)-map
  2. Check the adequacy of the total tumor size

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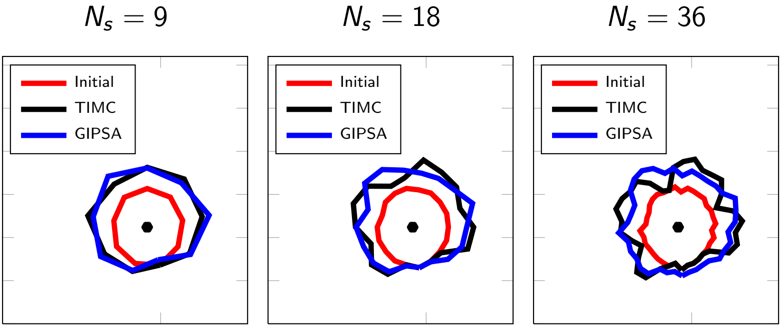
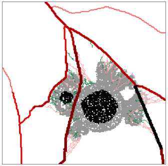
- For $N_s \in \{9, 18, 36\}$,
  1. Observe the final tumor form in the (x, y)-map
  2. Check the adequacy of the total tumor size

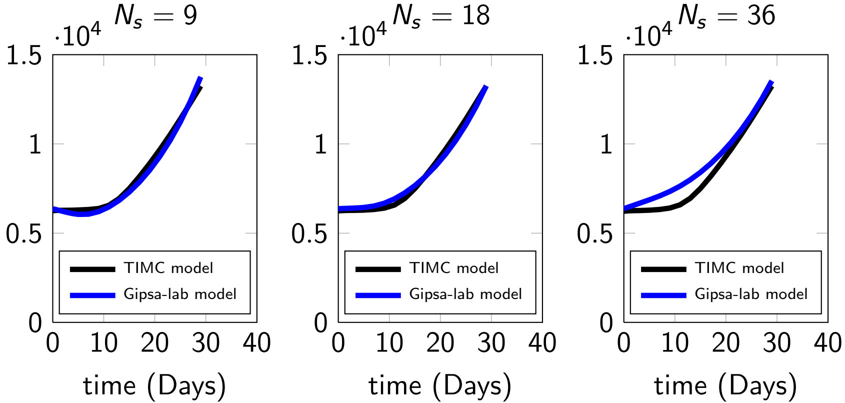
NOTA Changing N_s drastically changes the values of p in each sector as well as the corresponding vessels size. It represents a serious challenge for the model extrapolation capability.

Results


$N_s = 9$
Initial
TIMC
GIPSA
$N_s = 18$
Initial
TIMC
GIPSA
$N_s = 36$
Initial
TIMC
GIPSA



Results


$N_s = 9$
$N_s = 18$
$N_s = 36$
$\cdot 10^4$
1.5
1
0.5
0
0 10 20 30 40
time (Days)
TIMC model
Gipsa-lab model

Results

Erreur (%) on the total tumor size

$N_s = 9$	$N_s = 18$	$N_s = 36$
3.6%	-0.15%	2%

Computation times

Computation time for 30 Days scenario

$\mathbf{N_s = 9}$	$\mathbf{N_s = 18}$	$\mathbf{N_s = 36}$
50 ms	70 ms	120 ms

(Matlab / Mac PowerBook / 2.3GHz Intel Core i7)

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Derive a dynamic model that

1. depends on the 2D disposition of the vessels/tumor cells
2. is based on physiologically interpretable facts/conjectures
3. is computationally efficient for:
   - Extensive simulations
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Future works

- Introduce drug-effect in the dynamic model
- Model Analysis:
  - Observability
  - Sensitivity to parameters
- Identify using experiment-based data
- Use the model in MPC control design