Tumor growth model : case of liver metastasis (from GIST) and treatment resistance

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Metastases of GIST to the liver

GIST = Gastro Intestinal Stromal Tumor

- This type of cancer is currently not curable.
- Some « treatments exist » but eventually all fail.
- Two different therapeutical resistances are observed for these metastases.

Aim : Have a better understanding of this resistance thanks to a mathematical model.

Typical clinical case

Current course of action in a GIST :

1. first line : Glivec
2. second line : Sutent

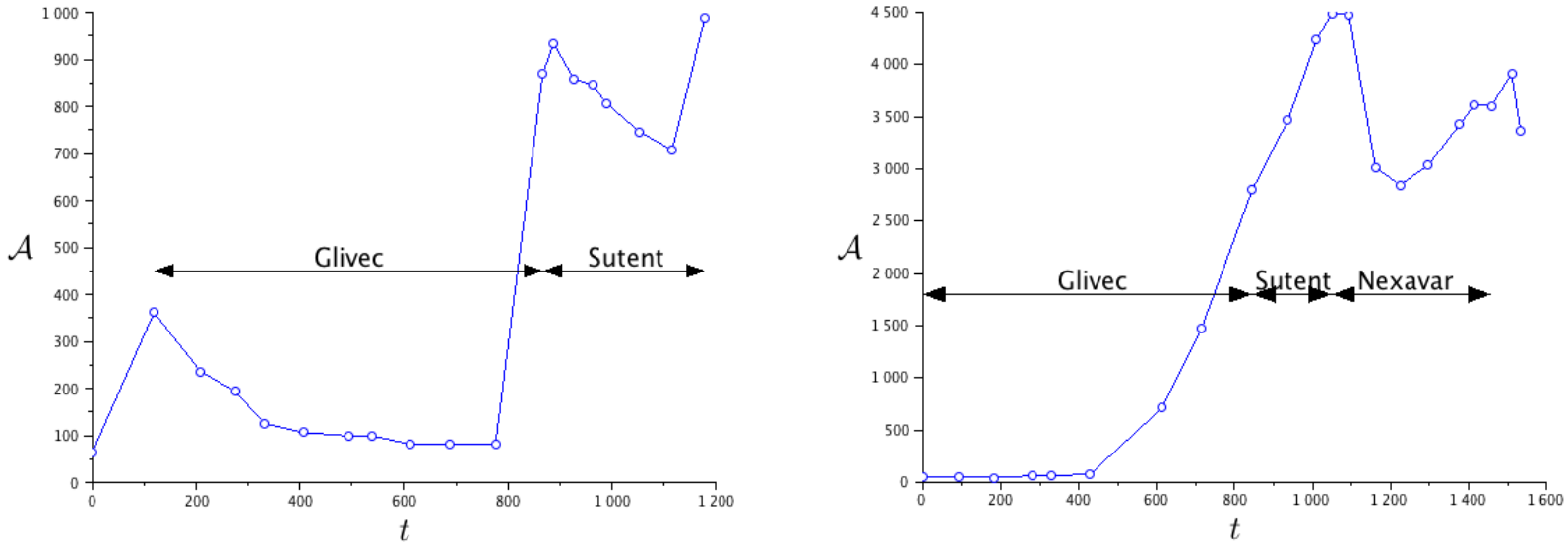


Figure: Typical evolution (in days) of tumor area (in mm^2) in case of treatment resistance

Typical clinical case

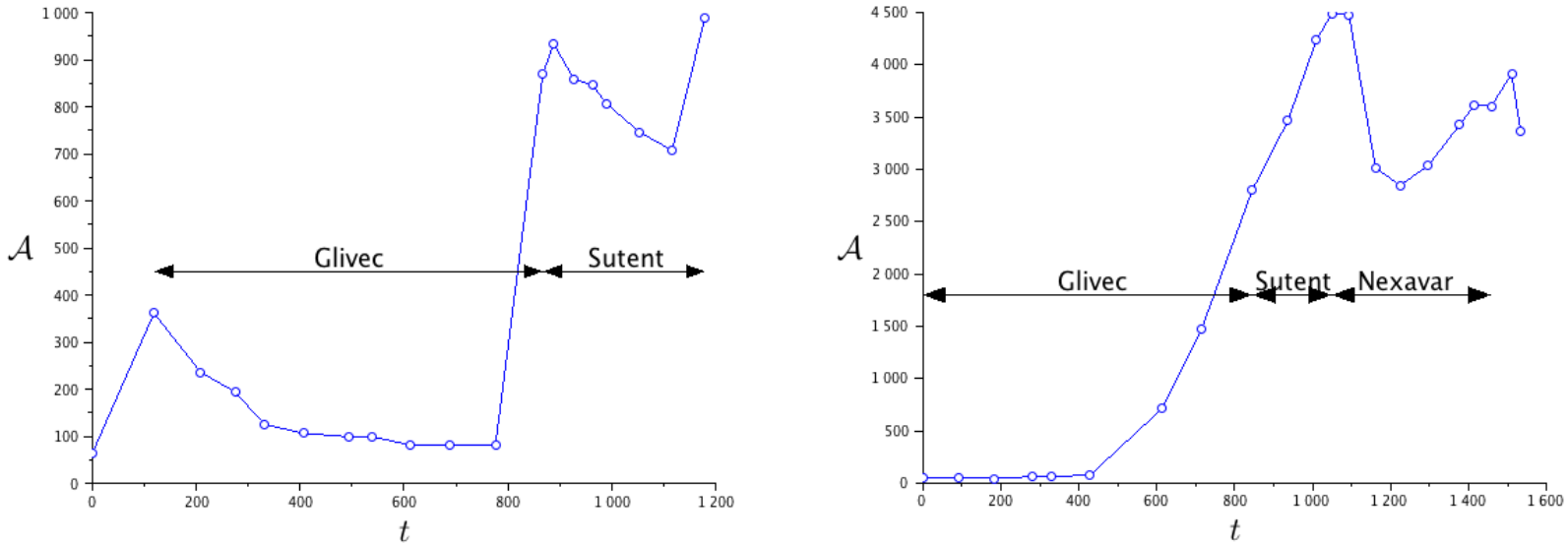


Figure: Typical evolution (in days) of tumor area (in mm^2) in case of treatment resistance

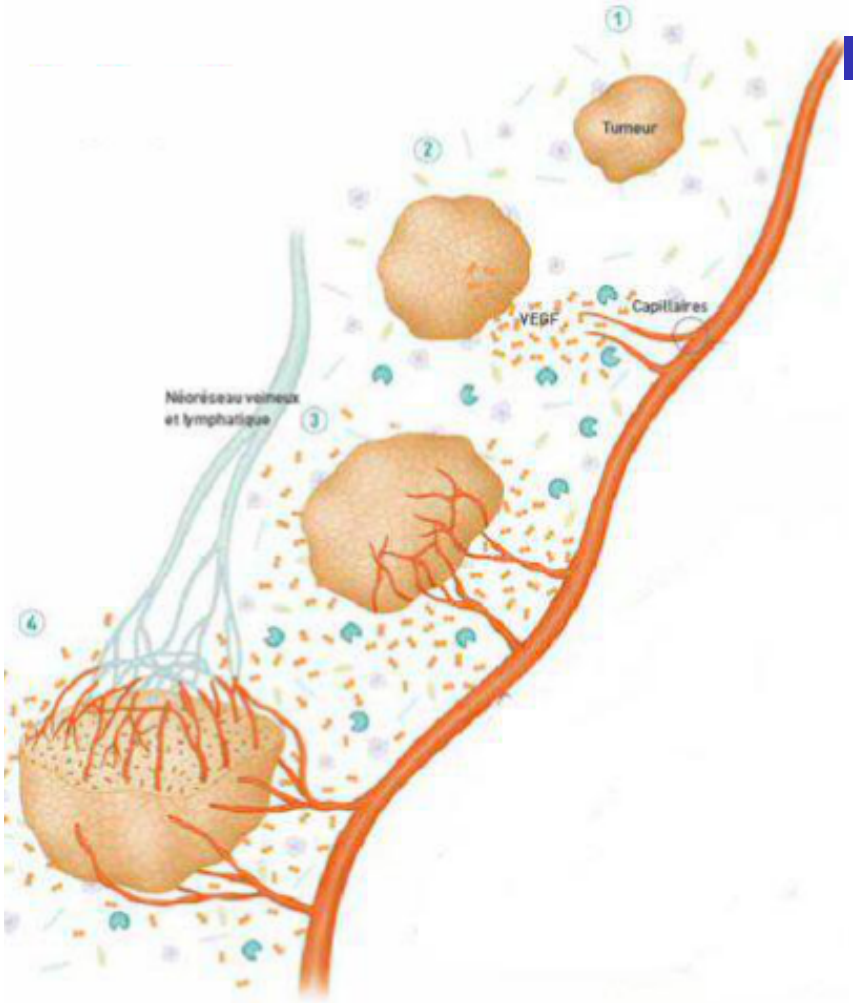
Aim : Get a model that take into account this 2 different type of drugs and these relapse.

Goals

Why create a mathematical model ?

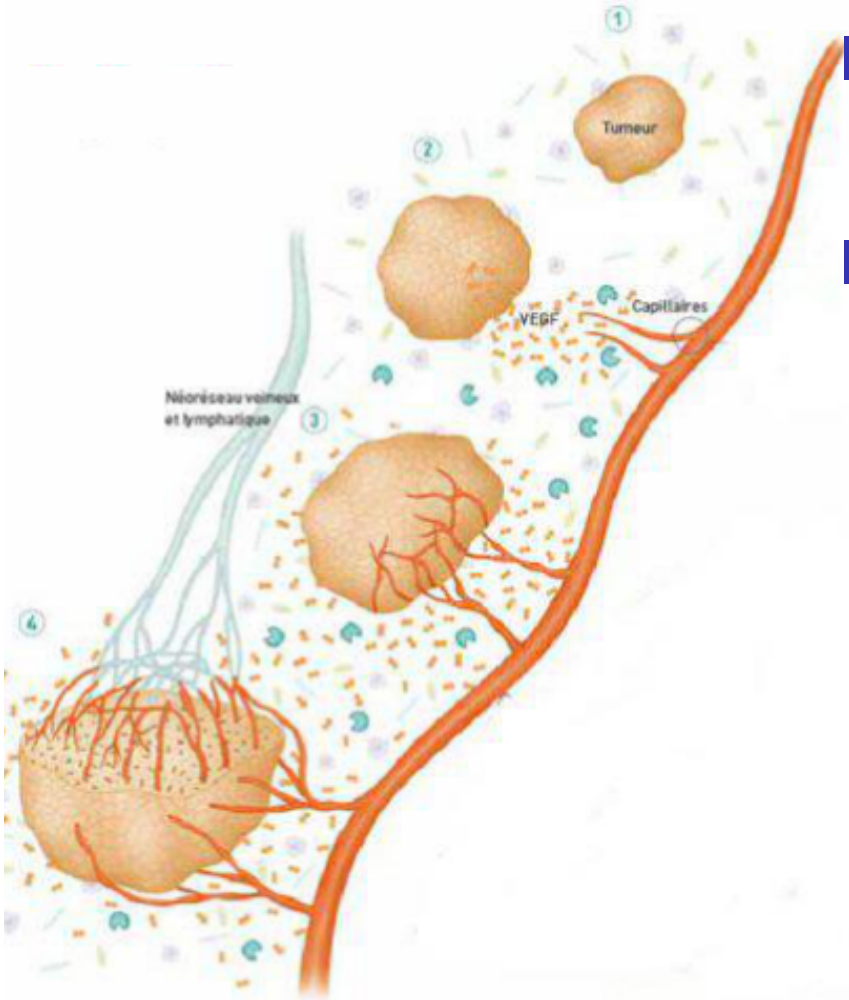
- To predict relapse
- To know when to change treatment
- To know if a treatment would be efficient or not
- To improve the medical knowledge about metastasis growth
- ...

Angiogenesis



1. Avascular stage : The tumor can grow with the current blood network that gives some nutrients.

Angiogenesis



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2. After a first growth, the blood network is no longer sufficient : nutrients missing from the tumor $\Rightarrow$ tumor cells secrete VEGF and other growth factor, that control the new blood vessel creation.

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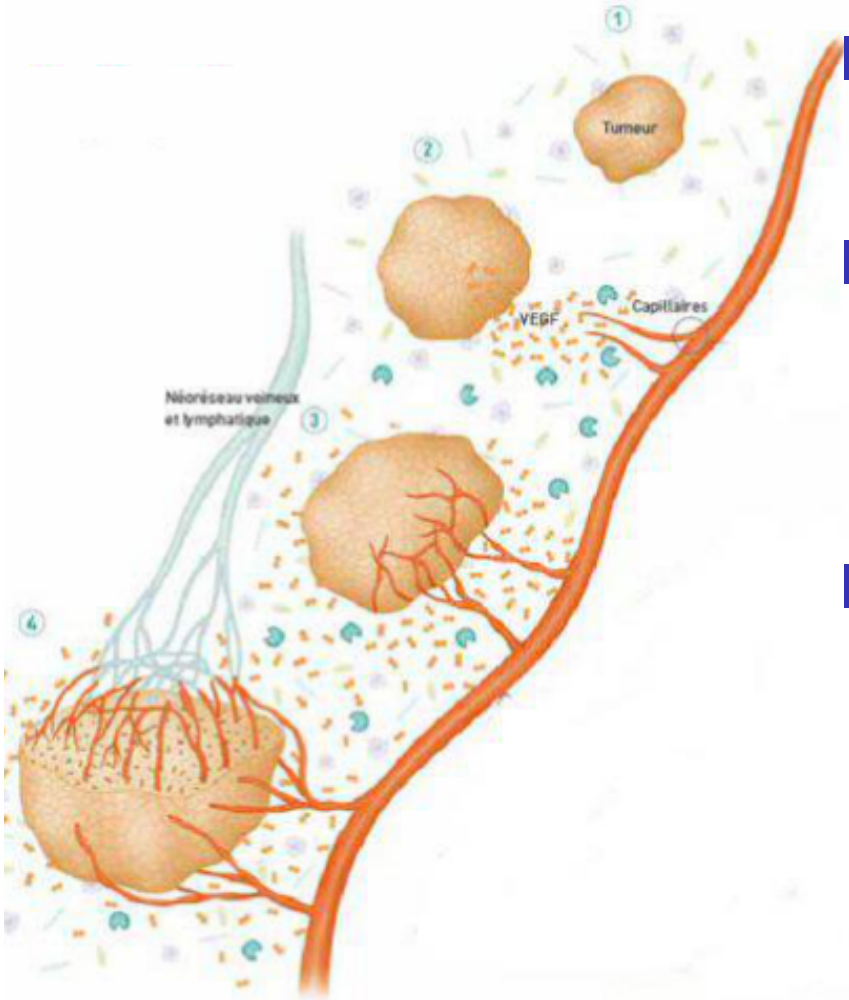

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3. The organism develops its blood network in direction of the VEGF concentration. The tumor is now in vascular stage.

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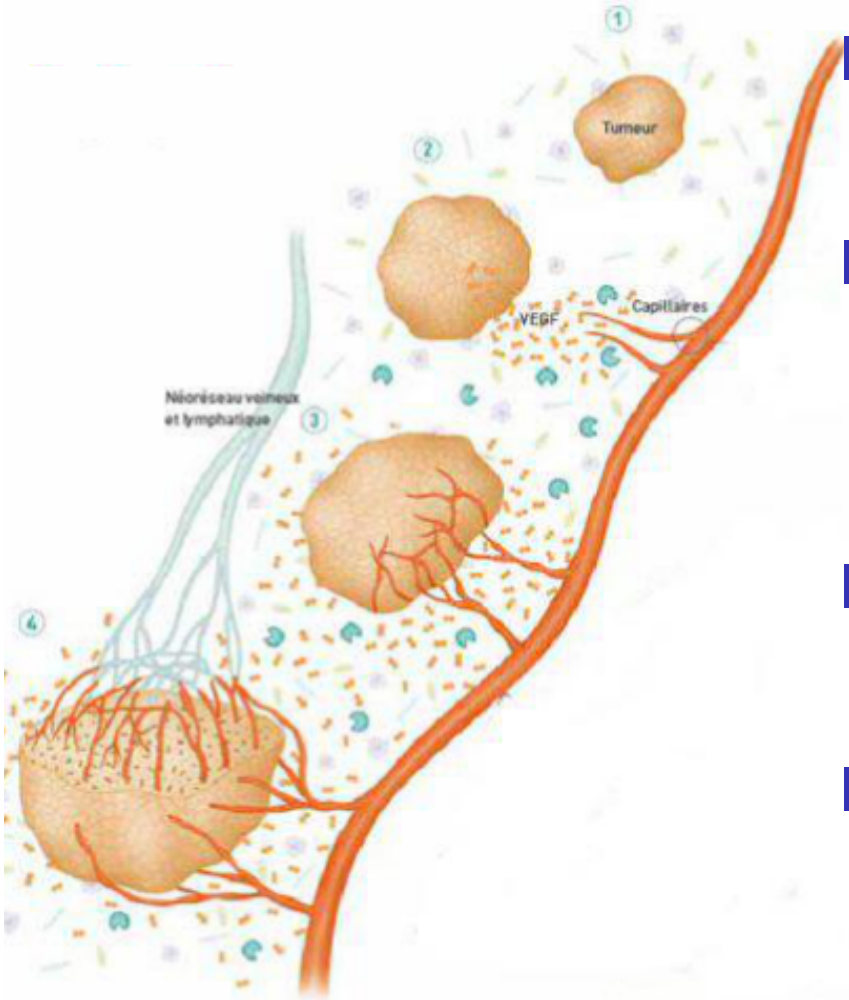

1. Avascular stage : The tumor can grow with the current blood network that gives some nutrients.
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4. The tumor continues to grow. It needs more and more nutrients and continue to secrete VEGF to increase the environmental vascularization.

Way of action of treatments

2 main drugs :

- The imatinib (Glivec) is a tyrosine-kinase inhibitor. It let the reactivation of apoptosis cycle.
- The sunitinib (Sutent) is a VEGF inhibitor. This drug targets a VEGF receptor and prevents the creation of new blood vessel.

$\Longrightarrow$ The model must take into account the angiogenesis.

The populations

$P_1(t,x)$: Tumor cells that are sensitive to Glivec and Sutent.

$P_2(t,x)$: Tumor cells that are not sensitive to Glivec but sensitive to Sutent.

$P_3(t,x)$: Tumor cells that are sensitive neither to Glivec nor to Sutent.

$N(t,x)$: Necrotic cells.

$S(t,x)$: Health tissue.

We assume that the flow is satured :

$$P_1 + P_2 + P_3 + N + S = 1. \tag{1}$$

Growth rate

$M(t,x)$: Blood flux ; vascularisation.

M_s : Hypoxia threshold.

γ_0, γ_1 : Constant coefficient of growth (and decreasing) rate of tumor cells depends on each patient.

$$\gamma_{pp}(M) = \frac{\gamma_0}{2}\Big(1 + \tanh\big(R(M - M_s)\big)\Big) \quad (2)$$

$$\gamma_{pd}(M) = \frac{\gamma_1}{2}\Big(1 - \tanh\big(R(M - M_s)\big)\Big) \quad (3)$$

$$\gamma_{sd}(M) = C_S\gamma_1 \max\Big(0, -\tanh\big(R(M - M_s)\big)\Big) \quad (4)$$

PDEs on populations

$$\partial_t P_1 + \nabla.(vP_1) = (\gamma_{pp} - \gamma_{pd})P_1 \tag{5}$$

$$\partial_t P_2 + \nabla.(vP_2) = (\gamma_{pp} - \gamma_{pd})P_2 \tag{6}$$
$$\partial_t P_3 + \nabla.(vP_3) = (\gamma_{pp} - \gamma_{pd})P_3 \tag{7}$$
$$\partial_t N + \nabla.(vN) = \gamma_{pd}(P_1 + P_2 + P_3) + \gamma_{sd}S \tag{8}$$

We assume that :

$$\partial_t S + \nabla.(vS) = -\gamma_{sd}S \tag{9}$$

By denoting $P = \sum_i P_i$ and by adding above equations, we obtain :

$$\nabla.v = \gamma_{pp}P \tag{10}$$

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— Elimination of necrosis

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PDEs on populations

$$\partial_t P_1 + \nabla.(vP_1) = (\gamma_{pp} - \gamma_{pd})P_1 - f(t)(1+M)P_1 - \nu(1-g(t))(1+M)P_1 \quad (5)$$

$$\partial_t P_2 + \nabla.(vP_2) = (\gamma_{pp} - \gamma_{pd})P_2 - \nu(1-g(t))(1+M)P_2 \quad (6)$$

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$$\partial_t N + \nabla.(vN) = \gamma_{pd}(P_1+P_2+P_3) + \gamma_{sd}S - \mu(1+M)N + f(t)(1+M)P_1 + \nu(1-g(t))(1+M)(P_1+P_2) \quad (8)$$

— Elimination of necrosis
— Action of Glivec $f(t)$
— Small cytotoxic action of Sutent $g(t)(\nu \sim 1\%)$

We assume that :

$$\partial_t S + \nabla.(vS) = -\gamma_{sd}S \quad (9)$$

By denoting $P = \sum_i P_i$ and by adding above equations, we obtain :

$$\nabla.v = \gamma_{pp}P - \mu(1+M)N \quad (10)$$

Angiogenesis

$$\partial_t \xi_1 = \alpha \int_\Omega \left(1, 1 - \frac{\gamma_{pp}}{\gamma_0}\right) (P_1 + P_2) g \mathrm{d}x - \lambda \xi_1 \quad (11)$$

$$\partial_t \xi_2 = \alpha \int_\Omega \left(1, 1 - \frac{\gamma_{pp}}{\gamma_0}\right) P_3 \mathrm{d}x - \lambda \xi_2 \quad (12)$$

By considering the sum, we have :

$$\partial_t \xi = \alpha \int_\Omega \left(1, 1 - \frac{\gamma_{pp}}{\gamma_0}\right) \left[(P_1 + P_2) g + P_3\right] \mathrm{d}x - \lambda \xi \quad (13)$$

$\xi_1(t)$: Average concentration of VEGF.

$\xi_2(t)$: Average concentration of others growth factors.

λ : Elimination rate of angiogenic signal.

α : Production rate of angiogenic signal.

Vascularization

$$\partial_t M - \xi \frac{\nabla S}{\|\nabla S\|} \nabla M = \underbrace{C_0 S \left(1 - \frac{M}{2M_s}\right)}_{\substack{\text{We impose} \\ M = 2M_s \text{ in} \\ \text{health tissue.}}} \overbrace{-\eta P M}^{\substack{\text{Destruction of} \\ \text{blood network caused} \\ \text{by tumor growth.}}} + \psi \Delta M$$

η : Destruction rate of blood network.

ψ : Rate of diffusion.

Notice that :

- More the angiogenic signal is important, more the vascularization is transported.
- The vascularization is transported from the health tissue to the tumor.

System closure

$\Pi(t,x)$: Pressure

$v(t,x)$: Global speed of cells induced by the pressure.

$k(t,x)$: Tissue permeability

Darcy's law :

$$v = -k\nabla\Pi \tag{14}$$

where :

$$k(t,x) = k_0 S + k_1 P + k_2 N \tag{15}$$

Fit of tumor area

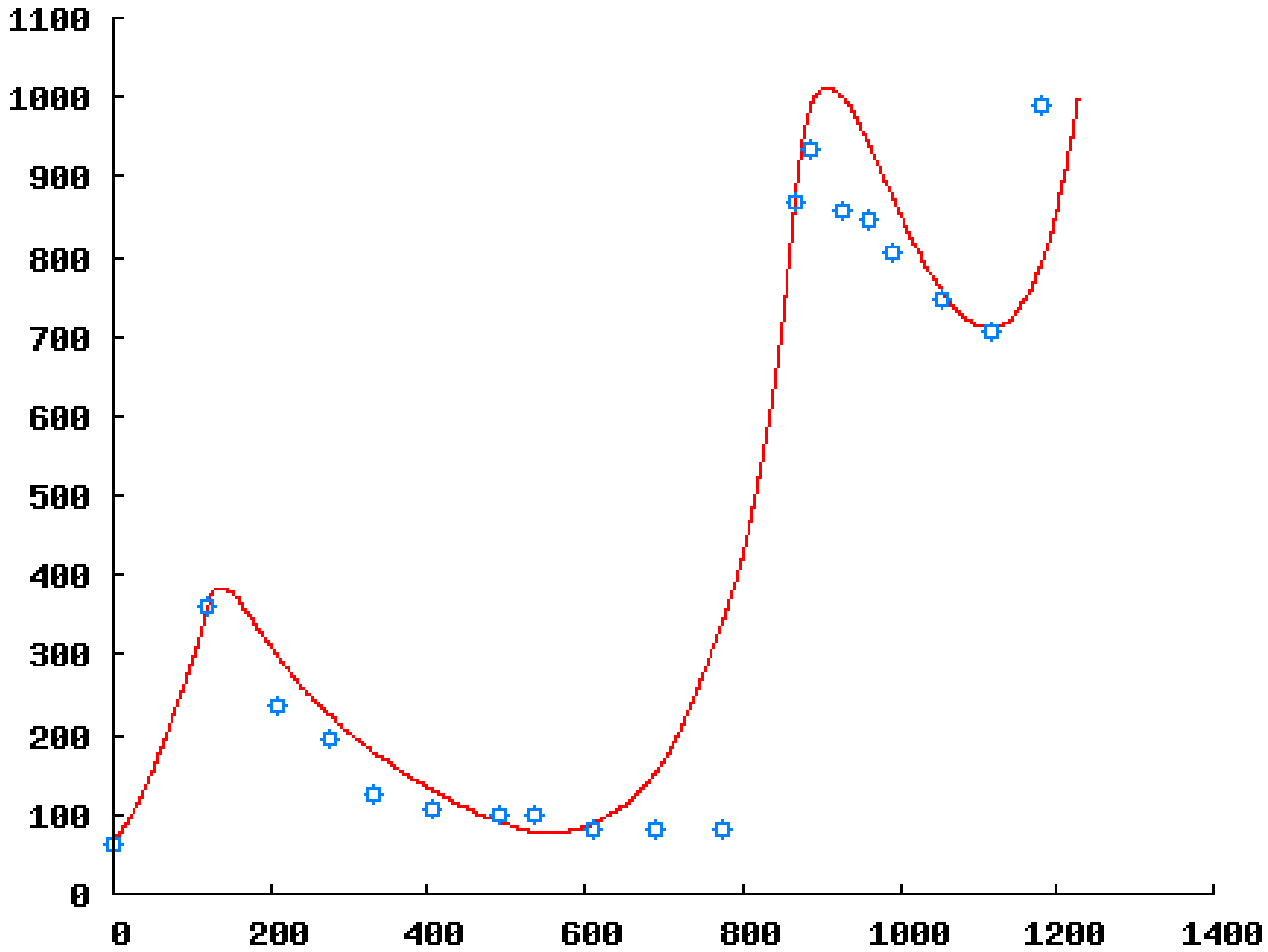
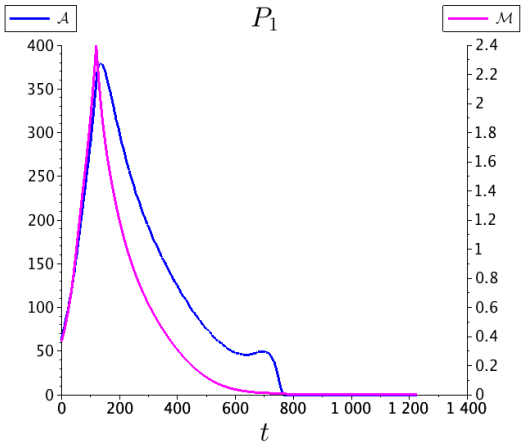
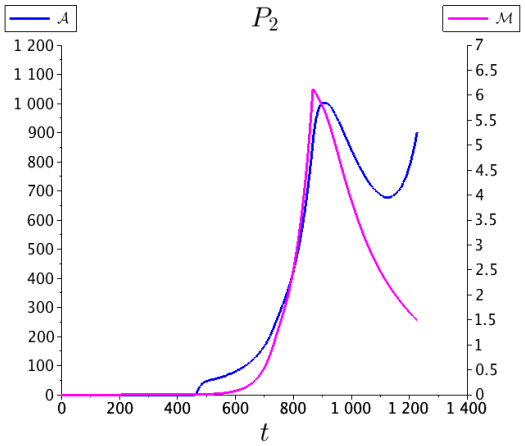
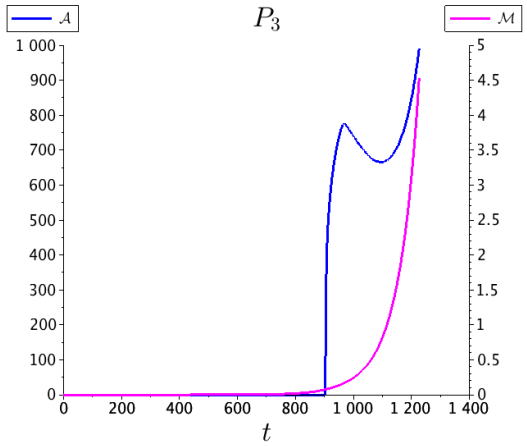


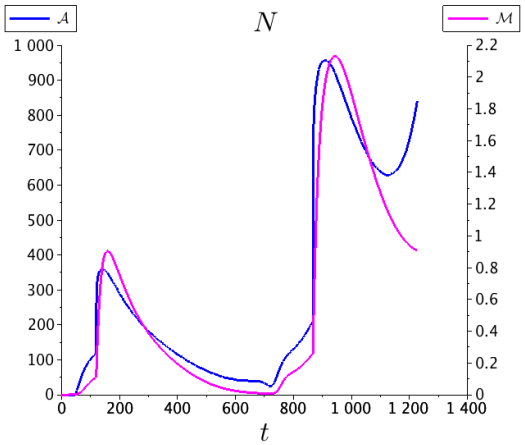
Figure: Tumor area (mm^2) in function of time (in days).

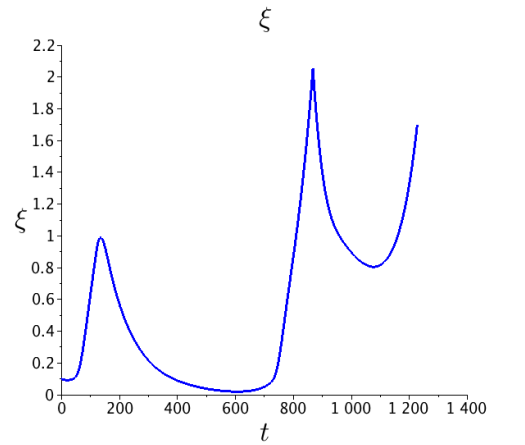
Evolution of cells populations

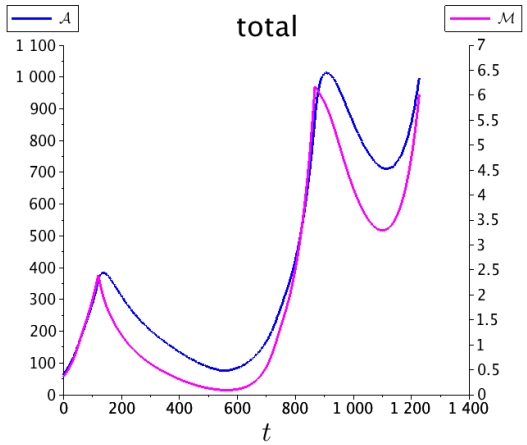




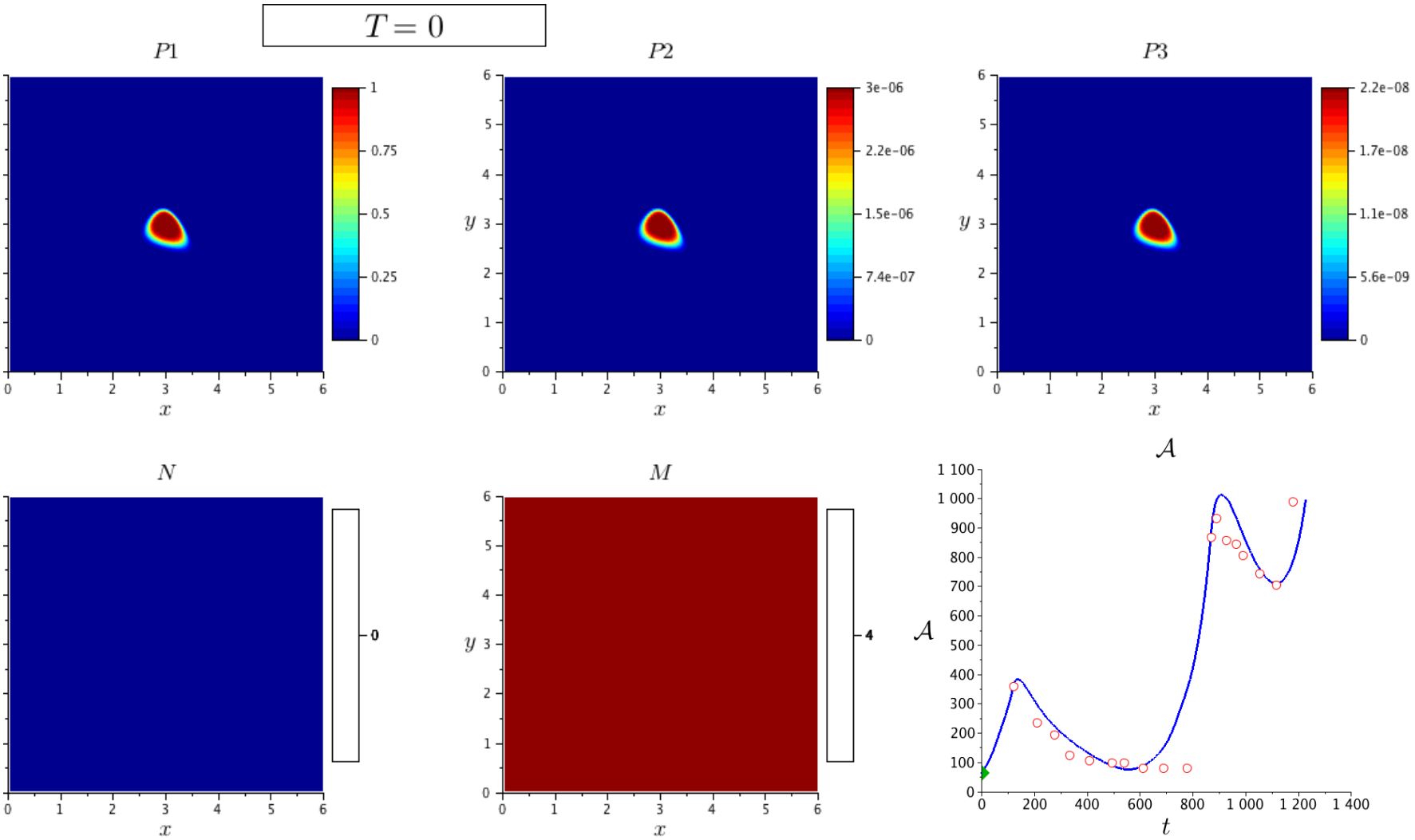




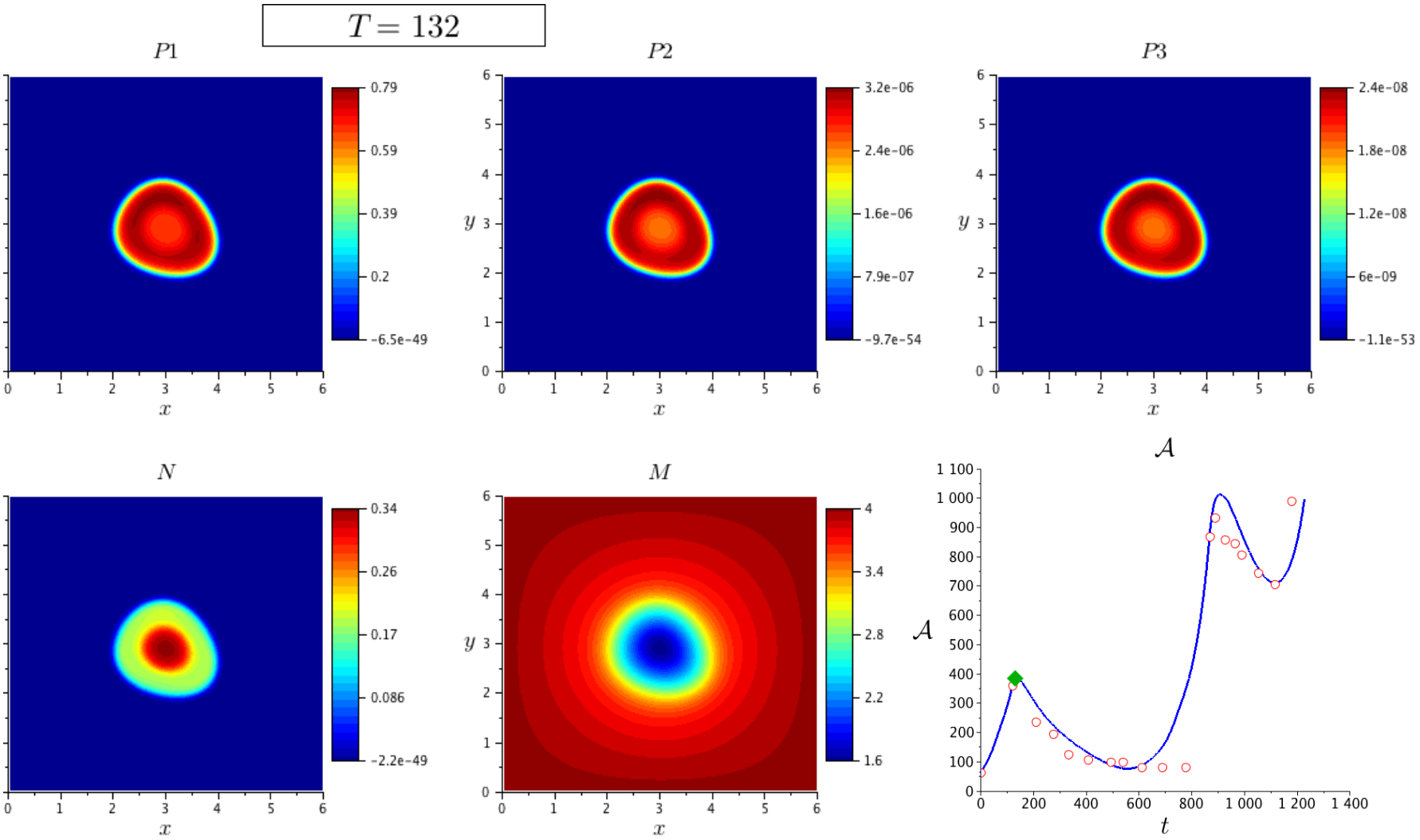




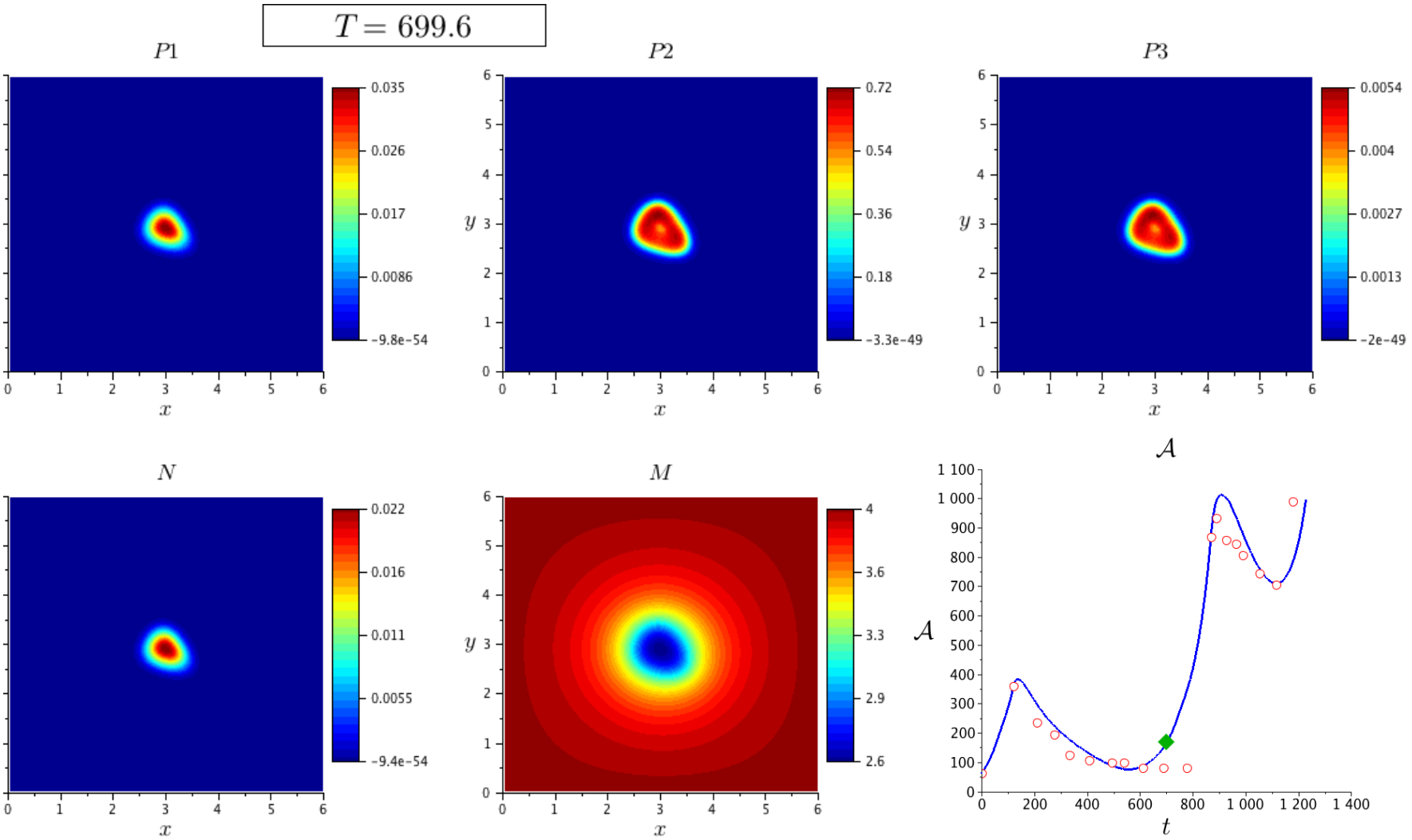
Initial growth



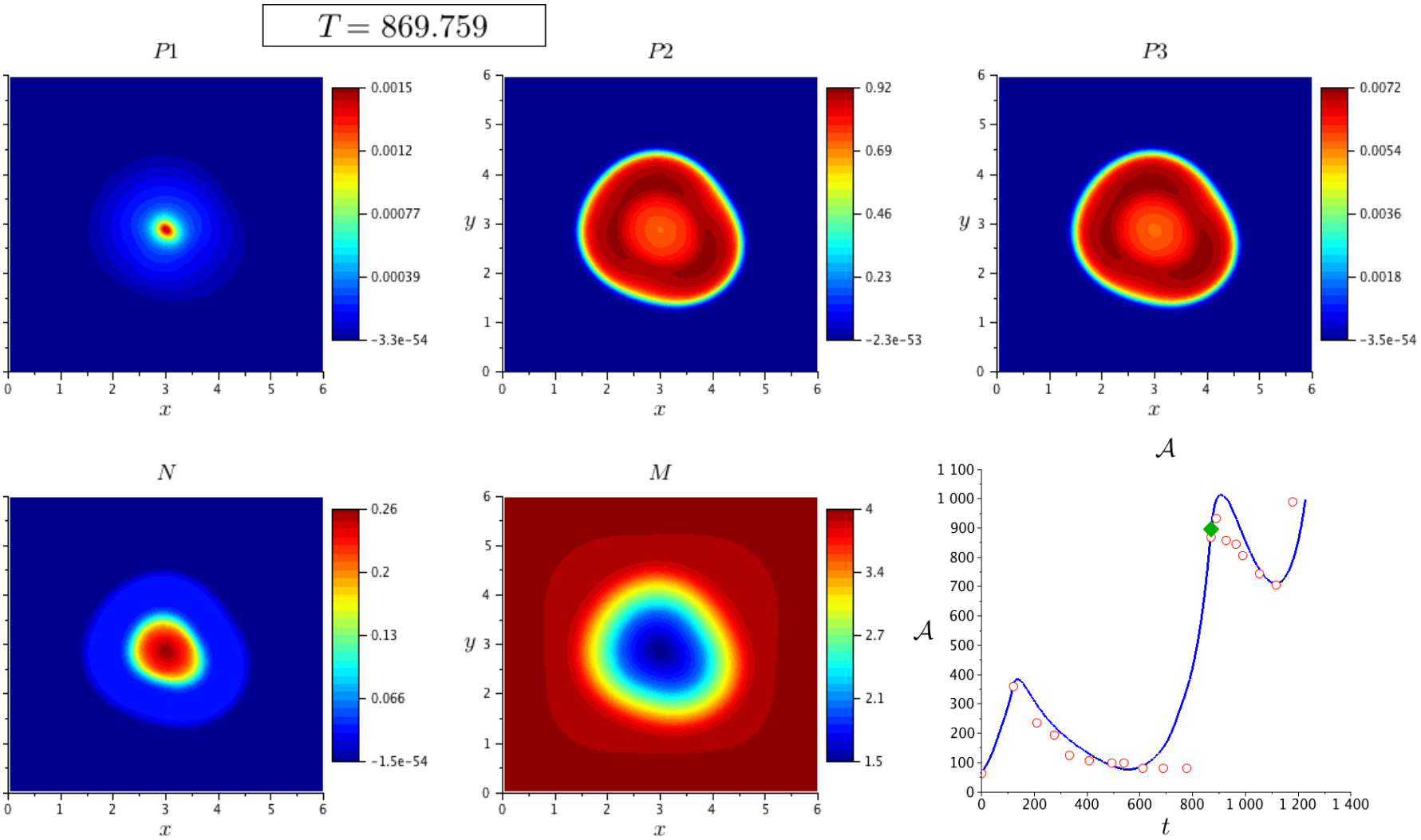
Glivec control



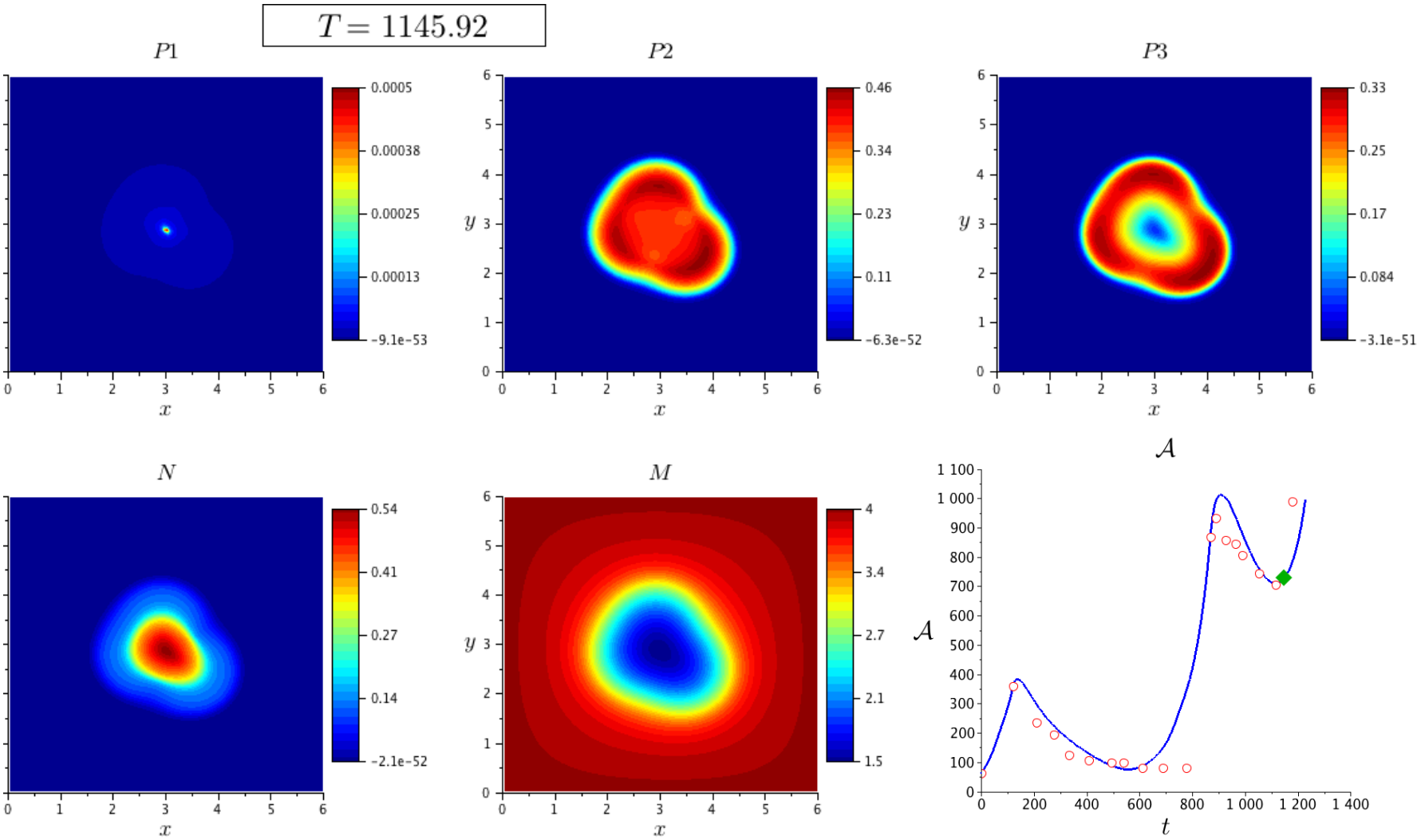
Relapse with Glivec



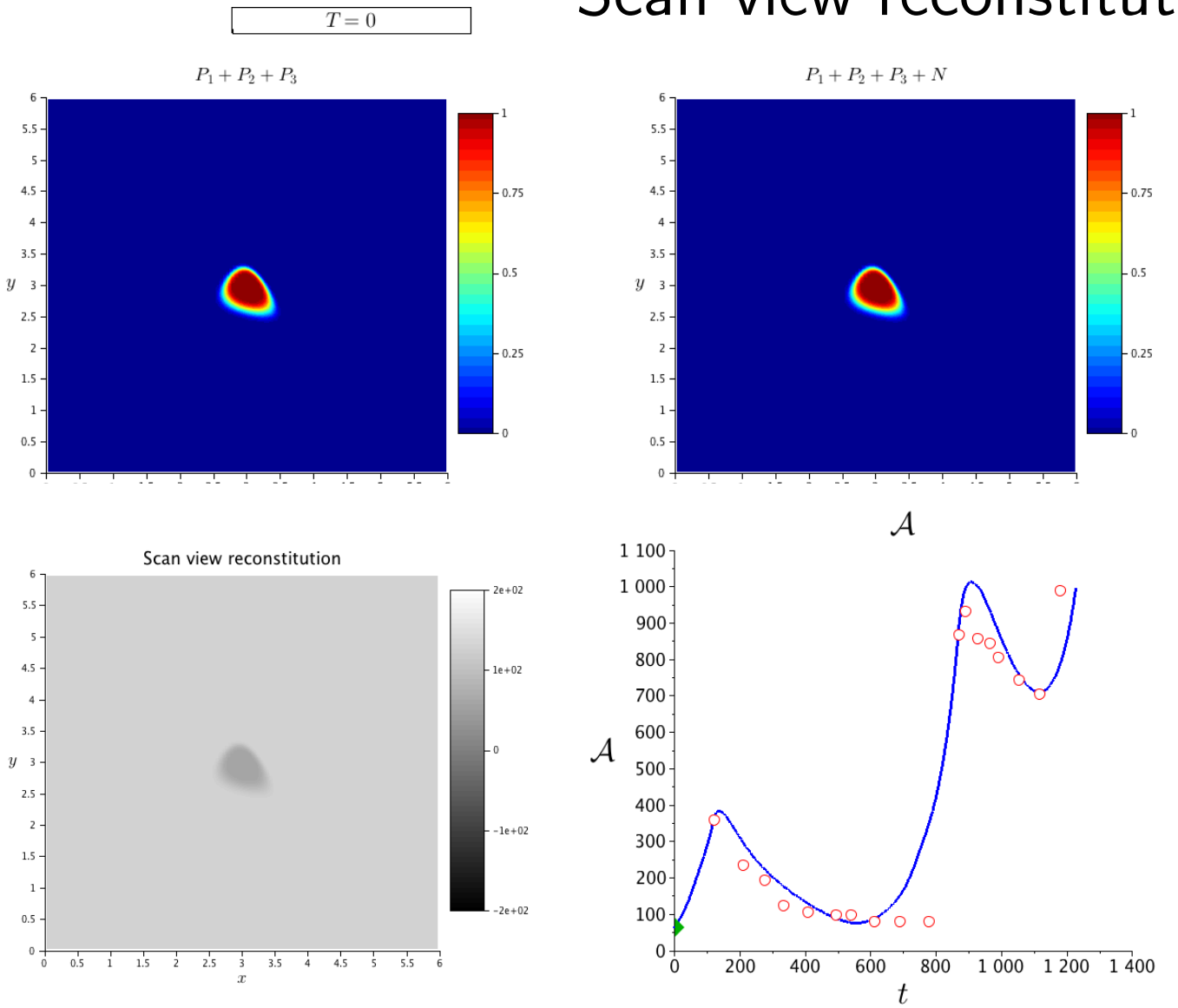
Sutent control



Relapse with Sutent



Scan view reconstitution



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Thanks for your attention.