Competition between cancer cells and T-cells under immunotherapy:

Evolutionary Biology and Mathematical Modelling

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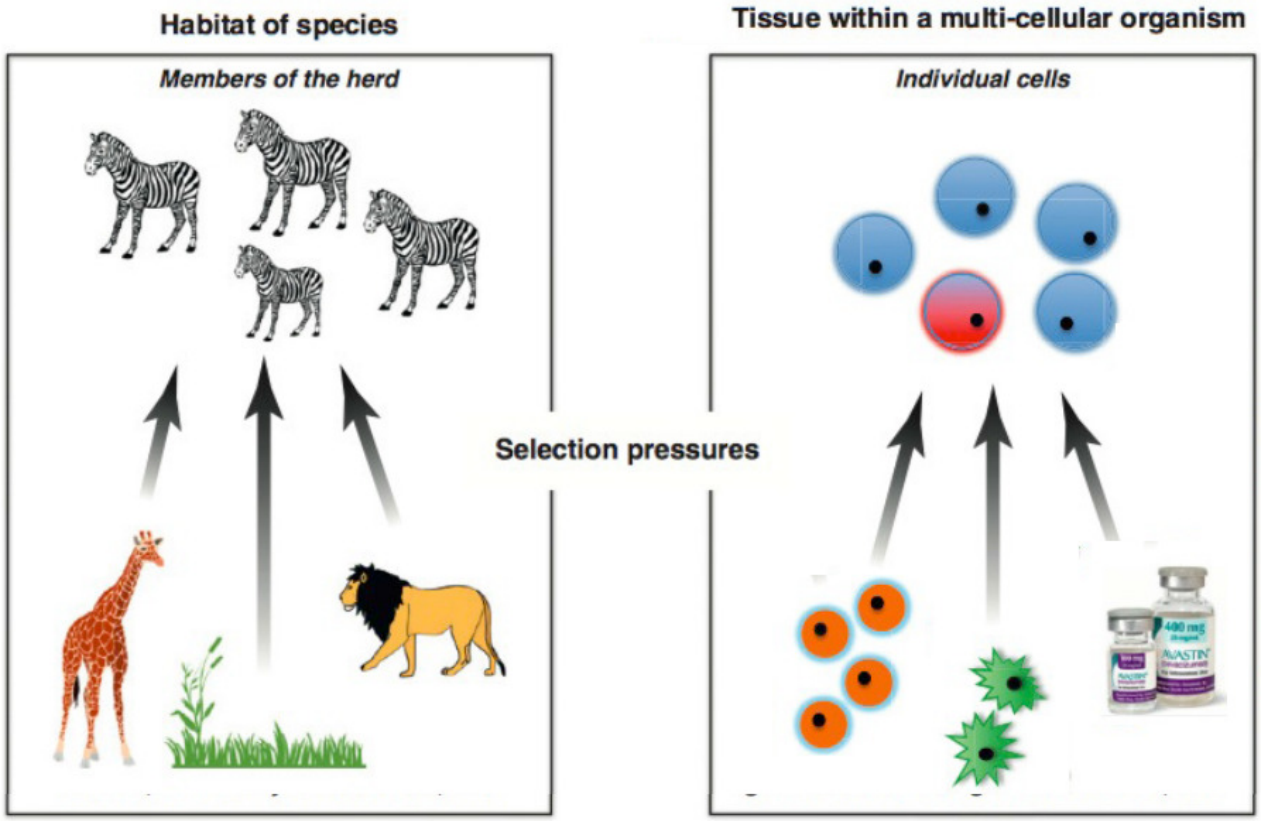
M. Delitala, T. Lorenzi, M. Melensi, A Mathematical Model of Competition between Cancer Cells and T-Cells under Immunotherapy, in Mathematical Modeling of Tumor-Immune System Dynamics, Eds. P. Kim, A. Eladdadi, Springer 2014.

Micro and Macro Systems in Life Sciences June 8-13, 2015, Bedlewo, Poland

Guidelines of the research

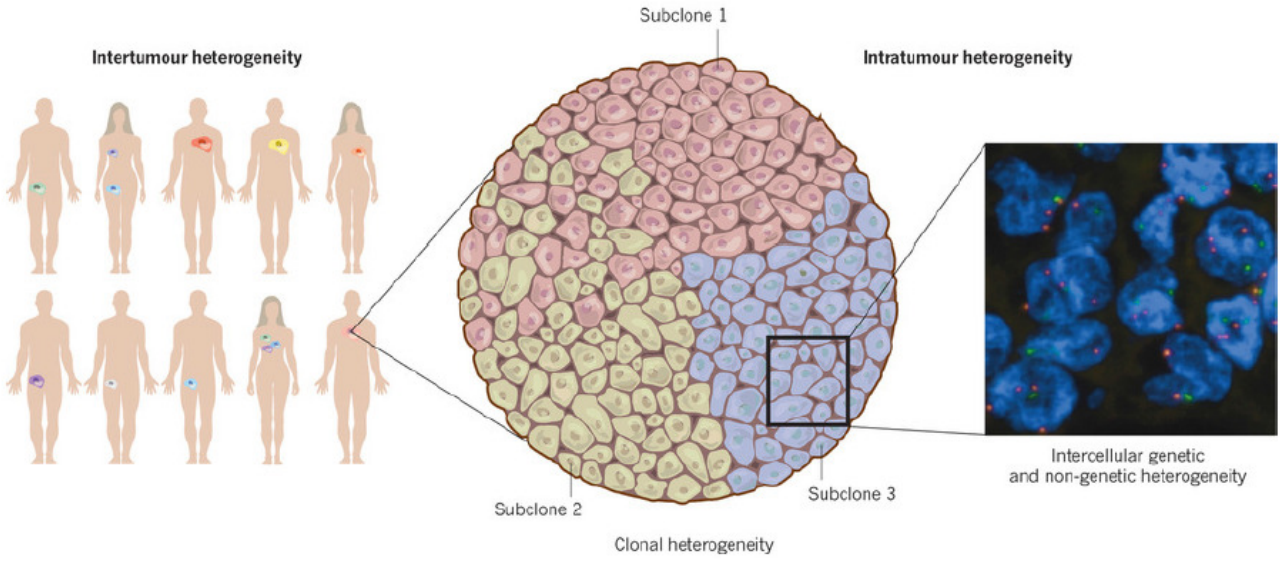
- Mathematical modelling of **complex living systems**.
- Many living beings and nonlinear interactions: the whole is more than the sum of its parts.
- **Virtual laboratories**: test hypothetical scenarios and enlighten stylized facts and **collective behaviors**, emerging from the complex interactions involved in the game.
- Focus on **evolutionary dynamics** in biology and medicine.

Evolutionary dynamics



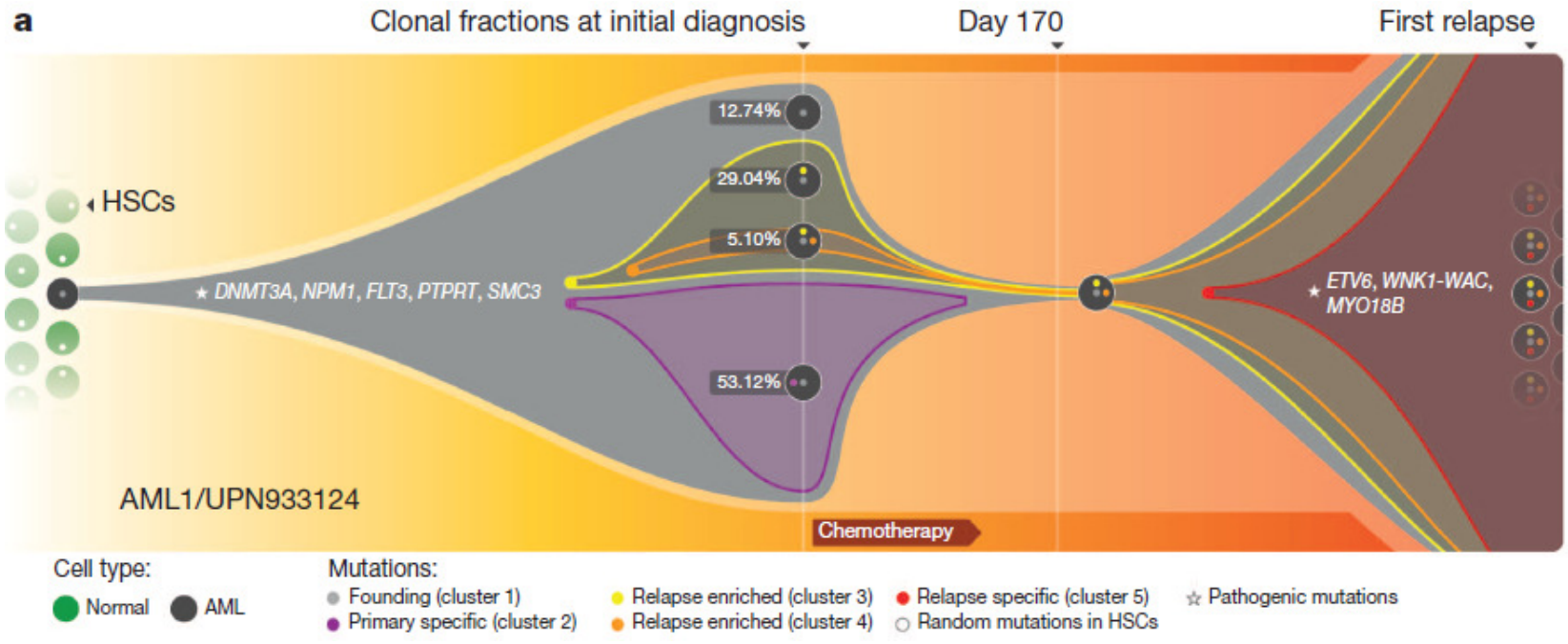
Evolution in ecology and selection at the cellular level.

Tumour heteogeneity



Intertumour heterogeneity: genetic and phenotypic variation are observed between tumours of different tissue and cell types, as well as between individuals with the same tumour type.
Intratumour heterogeneity: within a tumour, subclonal diversity may be observed.
R. A. Burrell et alii, The causes and consequences of genetic heterogeneity in cancer evolution, Nature 2013.

Clonal selection in tumours



Graphical representation of clonal evolution in AML (**Acute Myeloid Leukemia**) from the primary tumour to relapse with the selection of the resistant clones.
Li Ding et alii, Nature, 2012.

Cancer progression from an evolutionary perspective

- Tumor progression and development is a complex evolutionary process, see e.g. *Merlo et alii (2006)*.
- Diversity: aggregates **heterogeneously composed** of cells carrying different phenotypic expressions or mutations.
- **Competition for space and resources** (e.g. oxygen and glucose) among healthy and cancer cells within the environment defined by the surrounding tissues.
- The **fitness** (i.e. the ability to survive and reproduce) of neoplastic clones is shaped by different selective pressures that can vary in different micro-environment.
- Exposure to anti-cancer therapies and the predation by the immune system leads to **selection** of cells expressing highly resistant phenotypes.
- Clonal evolution shapes to a **Darwinian micro-evolution** generally selecting for increased proliferation and survival, and might lead to invasion, metastasis and therapeutic resistance.

Some references

- A.R.A. Anderson, A.M. Weaver, P.T. Cummings, V. Quaranta, Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment, *Cell*, (2006).
- D. Basanta, M. Simon, H. Hatzikirou, A. Deutsch, Evolutionary game theory elucidates the role of glycolysis in glioma progression and invasion, *Cell Proliferation* (2008)
- Bessonov, N.; Reinberg, N., Volpert, V. Mathematics of Darwin's diagram, *Mathematical Modelling of Natural Phenomena*, 2014
- R. A. Gatenby, A. S. Silva, R. J. Gillies, B. Roy Frieden, Adaptive therapy, *Cancer Res*, 2009.
- Lorz, A., Lorenzi, T., Hochberg, M.E., Clairambault, J., Perthame, B. Populational adaptive evolution, chemotherapeutic resistance and multiple anti-cancer therapies. *Mathematical Modelling and Numerical Analysis*, 2013.
- Wodarz, D. and Komarova. N.L. Computational Biology of Cancer: Lecture notes and mathematical modeling. *World Scientific Publishing*, (2005).

Role of the immune system

- ”Conceptual progress in the last decade has added two **emerging hallmarks** of potential generality to this list-reprogramming of energy metabolism and **evading immune destruction**.”
  D. Hanahan and R. A. Weinberg, Cell, (2011).
- ”Mutated cells on their way to giving rise to a tumor have also to learn how to thrive in a chronically inflamed microenvironment, **evade immune recognition**, and suppress immune reactivity”.
  F. Cavallo, C. De Giovanni, P. Nanni, G. Forni, and P.L. Lollini, Cancer Immunol. Immunother., (2011).

Some references

Several **mathematical models** of tumor-immune competition and of immune response have been proposed. Among others:

- A. Bellouquid, E. De Angelis, D. Knopoff, From the modeling of immune hallmarks of cancer to a bleak swan in biology, *Math. Mod. Meth. Appl. Sci.*, 2013.
- P. Kim, P. Lee, D. Levy, A theory of immunodominance and adaptive regulation, *Bull. Math. Biol.*, 73 (2011)
- LG. de Pillis, W. Gu, AE. Radunskaya, Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations, *Journal of Theoretical Biology*, 2006.
- U. Ledzewicz, A. d'Onofrio, H. Schattler, Tumor development under combination treatments with anti-angiogenic therapies, Mathematical methods and models in biomedicine - Lect. Notes Math. Model. Life Sci. Springer, New York, (2013).
- E. Terry, J. Marvel, C. Arpin, O. Gandrillon, F. Crauste, Mathematical model of the primary CD8 T cell immune response: stability analysis of a nonlinear age-structured system, *J. Math. Biol.*, 2012

Some inspiring references

- Cancer **immunoediting**: “The **immune system has a dual role**: it can prevent tumor formation, and, at the same time, it also functions to promote or select tumor variants with reduced immunogenicity facilitating tumor escape from immune destruction.”
  G. P. Dunn et alii, Nature Immunology, (2002).

- The selective recognition mechanisms and the **learning process** of immune cells. Learning does not occur at individual (cell) level while it is an **emergent collective property** of the immune system as a whole resulting from promotion, through the **clonal expansion**, of successful clones and as evolution of the expressed repertoire with respect to potential one.

Immunotherapies

- Immunotherapy and antigen-specific protocols to **boost** or restore the **ability of the immune system** to fight cancer.
- A propel cancer immunotherapy to the **forefront of cancer treatment** in the immediate near future. See e.g. *(Oncology Meets Immunology: The Cancer-Immunity Cycle, D. S. Chen et alii, Cell, 2013)* and *(Cancer immunotherapy comes of age, I. Mellman et alii, Nature, 2011)*.
- However, **no durable clinical improvements**. A possible reason: cytotoxic T-cells die quickly, so that immune response is not sustained and cancer eventually comes back.
- **Current research trends** include cancer vaccines aimed at inducing both **tumor-specific effector T-cells**, which can reduce the tumor mass, and tumor-specific **memory T-cells**, which can control tumor relapse providing the immune system with “memory" (*i.e.*, they quickly expand becoming activated T-cells upon re-exposure to their cognate antigen).

Questions

Questions for the modelling:

- Which **evolutionary dynamics of cancer cells** is driven by the pressure of the immune system?
- Can we explain intra-tumor **heterogeneity** in terms of cell adaptation to local conditions?
- Action of TCs over cancer cells, with particular reference to recognition and **learning processes**?
- How **immunotherapy** affects the evolutionary dynamics of cancer cells?
- Can we enhance the anti-cancer efficacy of T-cells by using different types of **immune boosters in combination**?

Modeling approach and populations

Mathematical methods and framework developed at the mesoscopic scale. **Structured populations dynamics**: the identical-individuals assumption is too restrictive. See e.g. *(Bellomo, Bianca, Delitala, Physics of Life Reviews, 2009)* and *Perthame, Transport equations in biology. Birkhuser (2007)*.

- Population of **cancer cells** characterized by heterogeneous antigenic expressions, structured by $u \in U \subset \mathbb{R}_+$: the **antigenic expression** or briefly traits of cancer cells.
- Population of **activated T-cells** structured by $v \in V \subseteq U$: those antigens that T-cells can effectively attack. Briefly, traits of T-cells.
- All cells are considered **homogeneously mixed** *i.e.*, a well-mixed sample and space effects are kept aside.
- Action of **immunotherapies** aimed at boosting the proliferation of activated T-cells and immune memory.

Densities

- **Density functions** of cancer cells and T-cells with traits u and v respectively:

$$f_C = f_C(t,u) : [0,T] \times U \to \mathbb{R}^+, \qquad f_I = f_I(t,v) : [0,T] \times V \to \mathbb{R}^+.$$

- **Total densities** computed as momentum:

$$\varrho_C(t) = \int_U f_C(t,u)du, \qquad \varrho_I(t) = \int_V f_I(t,v)dv.$$

- **Infusion rates** of therapeutic agents boosting clonal expansion and immune memory at time $t \in [0,T]$:

$$c_P(t) \geq 0 \quad \text{and} \quad c_M(t) \geq 0$$

Evolution equations

$$\frac{\partial}{\partial t} f_C(t,u) = \underbrace{\left(\kappa_C - \mu_C \varrho_C(t)\right) f_C(t,u)}_{\text{cancer growth and cell competition}} \underbrace{- f_C(t,u) \int_V \eta_{\theta_I}(|u-v|) f_I(t,v) dv}_{\text{immune competition}}$$

$$\frac{\partial}{\partial t} f_I(t,v) = \underbrace{\left[\int_U \eta_{\theta_E}(|u-v|) f_C(t,u) du + \kappa_P c_P(t)\right] f_I(t,v)}_{\text{clonal expansion and boosting of T-cell proliferation}}$$
$$\underbrace{- \frac{\mu_I}{1+\mu_M c_M(t)} \varrho_I(t) f_I(t,v)}_{\substack{\text{homeostatic regulation and} \\ \text{boosting of immune memory}}}$$

Therapeutic agents: the dynamics of $c_P(t)$ and $c_M(t)$ are supposed to be given.

Parameters of the model

Biological Phenomena	**Parameters**
Tumor cell proliferation	κ_C
Cancer competition for resurces	μ_C
Immune competition	θ_I
Homeostatic regulation	μ_I
Selectivity clonal expansion	θ_E
Boosting of T-cell proliferation	κ_P
Boosting of immune memory	μ_M

Computational analysis: Settings

Numerical simulations are performed in MATLAB. $U = V := [0, 1]$ and implicit-explicit finite difference scheme with 400 points on the interval $[0, 1]$. Time domain: $[0, T]$, where $T = 1200dt$ and $dt = 0.1$.

- **Selectivity** of clonal expansion and immune competition:

$$\eta_{\theta_E}(|u - v|) := e^{-\theta_E|u-v|^2} \qquad \eta_{\theta_I}(|u - v|) := e^{-\theta_I|u-v|^2}$$

- Parameters set with an **explorative aim** to addres the above mentrioned questions:
  - $\kappa_{C,P} := 1$, tumor cell proliferation and boosting of T-cell proliferation.
  - $\mu_{C,I} := 0.5$, cancer competition for resurces and homeostatic regulation.
  - $\theta_{E,I} := 1000$, selectivity clonal expansion and of immune competition.
  - $\mu_M := 1$, boosting of immune memory.

Parameter setting

- c_P and c_M mimic different infusion schedules.
- **Initial conditions**

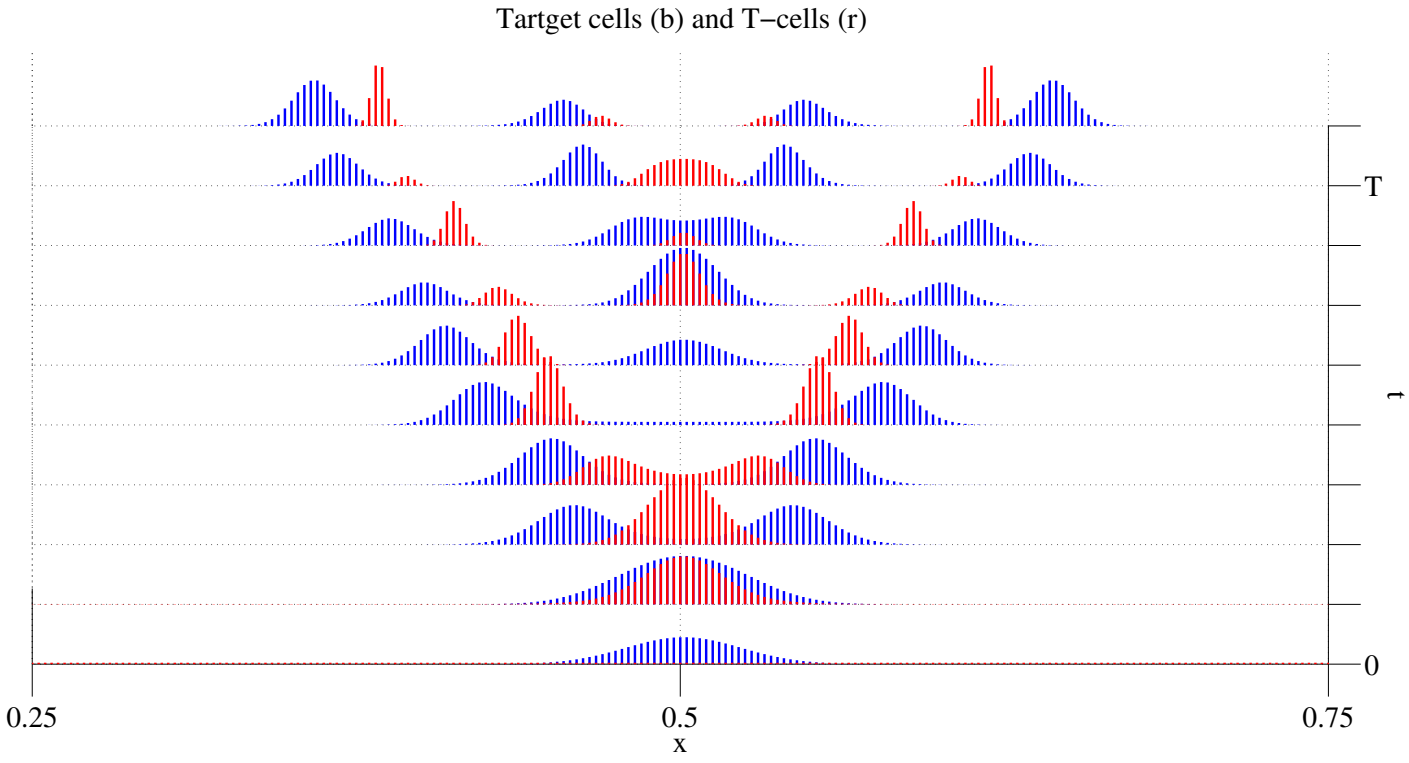
$$f_C(t=0,u) = C_C e^{-\frac{(u-0.5)^2}{0.001}}, \qquad f_I(t=0,v) = C_I \chi_V(v)$$

where χ_V is the characteristic function of the V set and $C_{C,I} \in \mathbb{R}_+$ such that

$$\varrho_{C,I}(t=0) \approx 1.$$

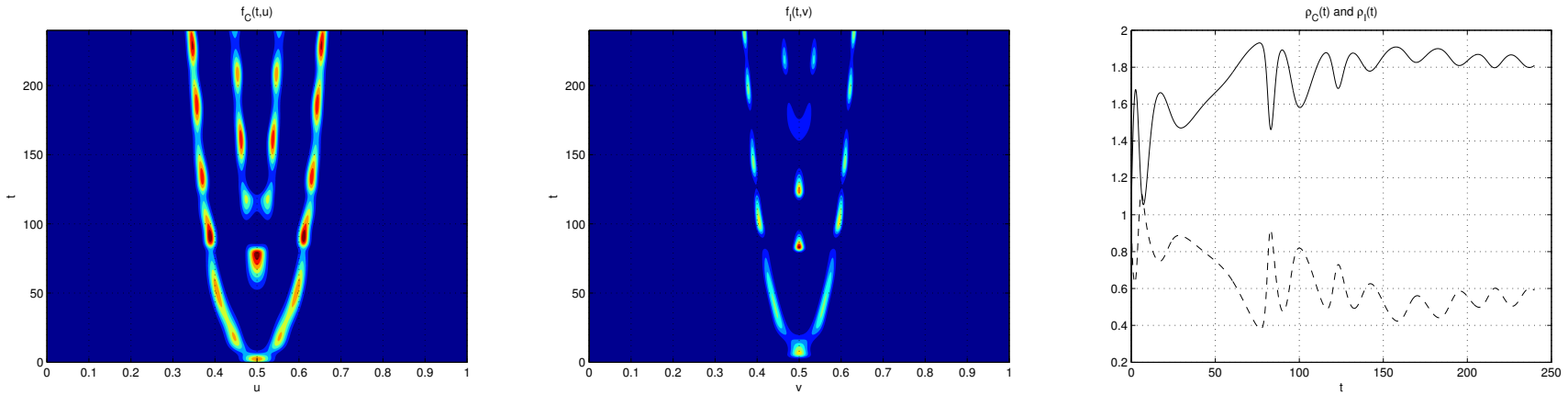
Cancer cell population is almost **monomorphic** at the beginning of observations (*i.e.*, most of the cancer cells are characterized by the same antigenic expression), while the same number of **activated T-cells** are found inside the system **for each possible antigenic expression** of cancer cells.

Dynamics of cancer cells without immunotherapies



"**Chase-and-escape**" dynamics involving activated T and cancer cells.

“**Branching process**" involving activated T and cancer cells.



$c_{P,M}(t) := 0$. Evolution of $f_C(t, u)$ (left panel), $f_I(t, v)$ (center panel), $\varrho_C(t)$ (right panel, solid line) and $\varrho_I(t)$ (right panel, dashed line).

- **Clonal expansion** leads to a proliferation of the T-cells that can effectively recognize and attack the antigens mostly expressed by the cancer cell population.
- The selective pressure exerted by activated T-cells causes the selection of those cancer cells that are actually able to evade immune predation: **tumor escape**.
- From the **evolutionary perspective**, immune competition pushes the monomorphic cancer cell population to become, in succession, dimorphic, trimorphic and then tetramorphic (*i.e.*, most of the cells are characterized by two, three or four given antigenic expressions, respectively).
- The immune system may introduce an additional selective pressure, which **reinforces the selection for the most fitting**, and then most resistant, **clones** and promoting the growth of tumor cell variants with increasing capacities to survive immune attack. In one word: immune system can select for resistance.

- These results are consistent with considerations drawn in some previous works on the **immunoediting**, *(G. P. Dunn et alii, 2002)* and more in general on the action of external pressures *(Merlo et al., 2006)* or of targeted therapeutic agents e.g. *(R. J. Gillies, D. Verduzco, R. A. Gatenby, 2012).*
- The same pattern of evolution of cancer cells is followed by T-cells with a certain delay, time required to adapt to the antigenic distribution of cancer cells. $f_I(t, v)$ replicates after a delay time the distribution of $f_C(t, u)$ over U. This adaptation can be view as a **collective learning** of the immune system as a whole resulting from promotion, through the clonal expansion, of successful clones, see also *M. Delitala and T. Lorenzi, DCDS-b, 2013*

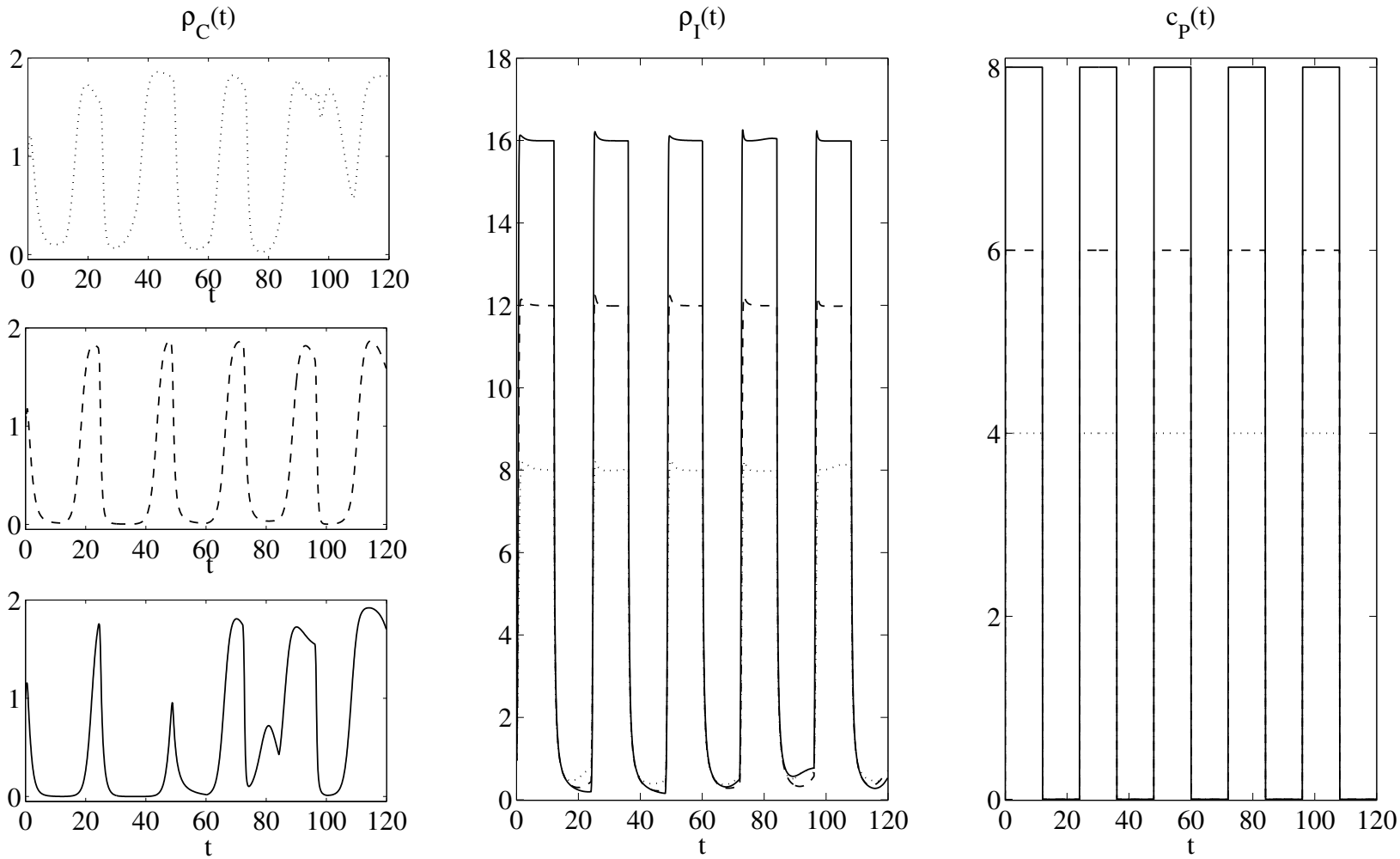
Effects of boosters on cancer dynamics

Evolution of cancer cells

- in presence of boosters of T-cell proliferation only,
- in presence of boosters of immune memory only,
- when therapeutic agents that boost T-cell proliferation and immune memory are simultaneously delivered.

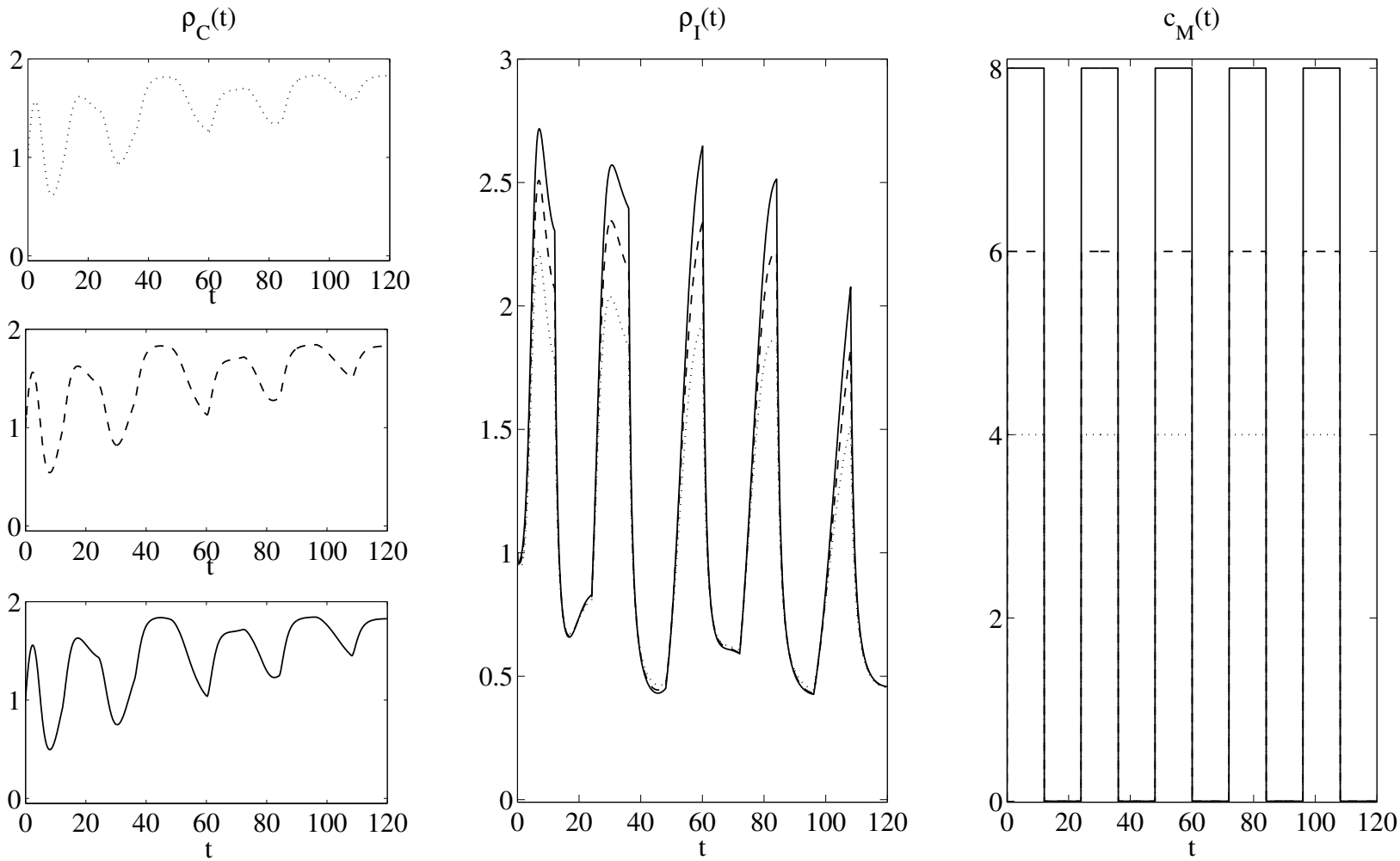
During simulations we choose periodic injections $\omega = 10\pi/T$, with three different delivered doses $C \in \{4, 6, 8\}$.

Effects of boosters of T-cell proliferation on cancer dynamics



$c_P(t) := Csgn(\sin(\omega t))^+$, $c_M(t) := 0$:. Evolution of $\varrho_C(t)$, $\varrho_I(t)$ and $c_P(t)$ for $C = 4$ (dotted lines), $C = 6$ (dashed lines) and $C = 8$ (solid lines).

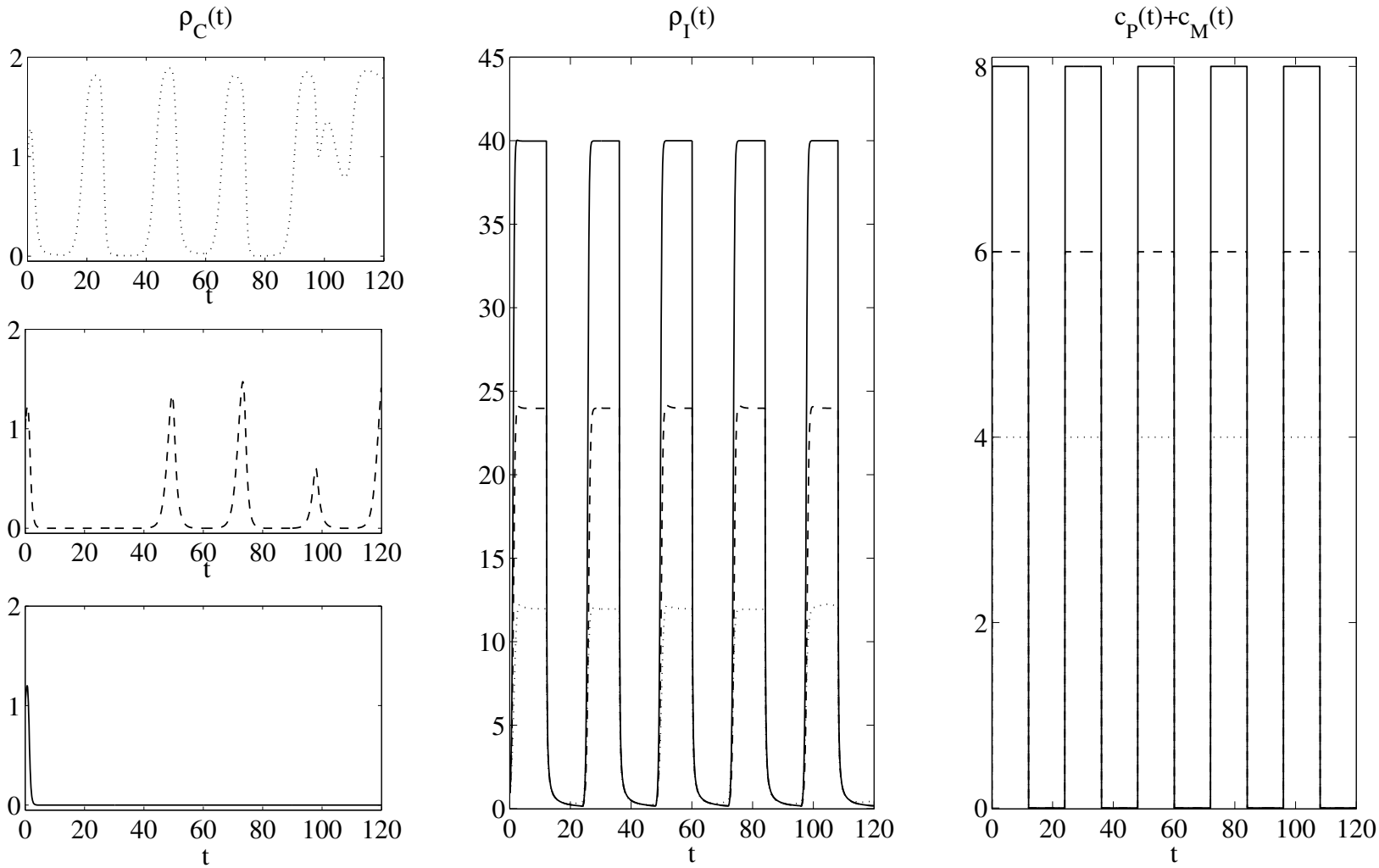
Effects of boosters of immune memory on cancer dynamics



$c_P(t) := 0, \quad c_M(t) := C sgn(\sin(\omega t))^+$. Evolution of $\varrho_C(t)$, $\varrho_I(t)$ and $c_M(t)$ for $C = 4$ (dotted lines), $C = 6$ (dashed lines) and $C = 8$ (solid lines).

- **Boosters of T-cell proliferation** allow only a temporary reduction of the concentration of cancer cells and do not allow the permanent eradication of cancer cells.
- **Boosters of immune memory** leaves the qualitative dynamics of the cancer cell density almost unaltered with respect to the case without therapies and do not allow the permanent eradication of cancer cells.

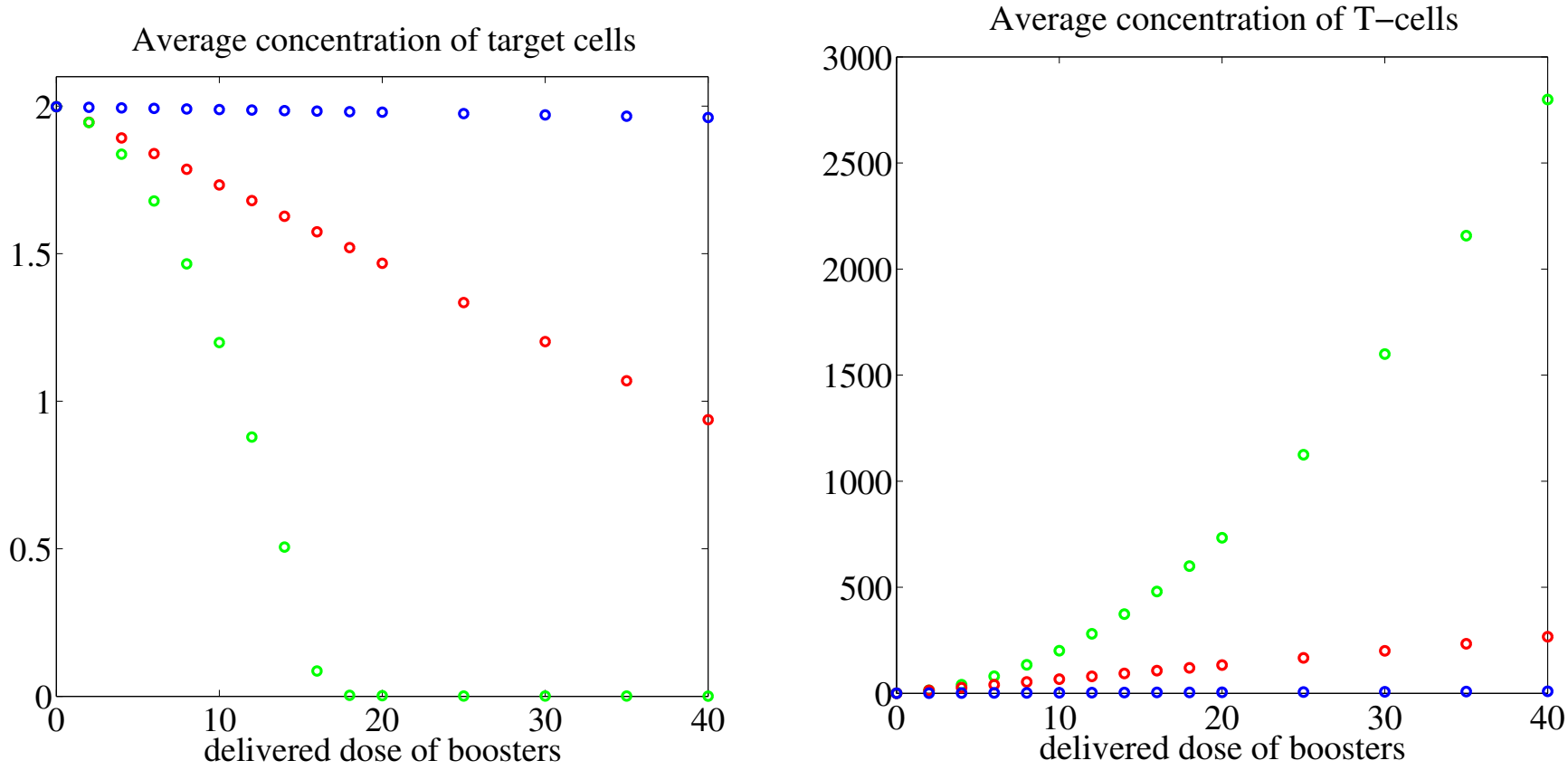
Joint action of boosters of T-cell proliferation and immune memory



$c_P(t) := \frac{C}{2}\, sgn(\sin(\omega t))^+, \quad c_M(t) := \frac{C}{2}\, sgn(\sin(\omega t))^+$. Evolution of $\varrho_C(t)$, $\varrho_I(t)$ and $c_P(t) + c_M(t)$ for increasing values of the amount of therapeutical agent at each injection: $C = 4$ (dotted lines), $C = 6$ (dashed lines) and $C = 8$ (solid lines).

- If the two types of immune boosters under consideration are used in combination, there exist certain doses that make possible to push the **cancer cell population toward extinction** (left bottom panel).
- Concentration of cancer cells (left panels) is progressively reduced and **tumor relapse is progressively controlled** as long as the delivered doses are increased.
- These results lead us to conclude that **more effective** immunotherapy protocols can be designed using suitable **combinations of therapeutic agents** that boost T-cell proliferation and immune memory as well.

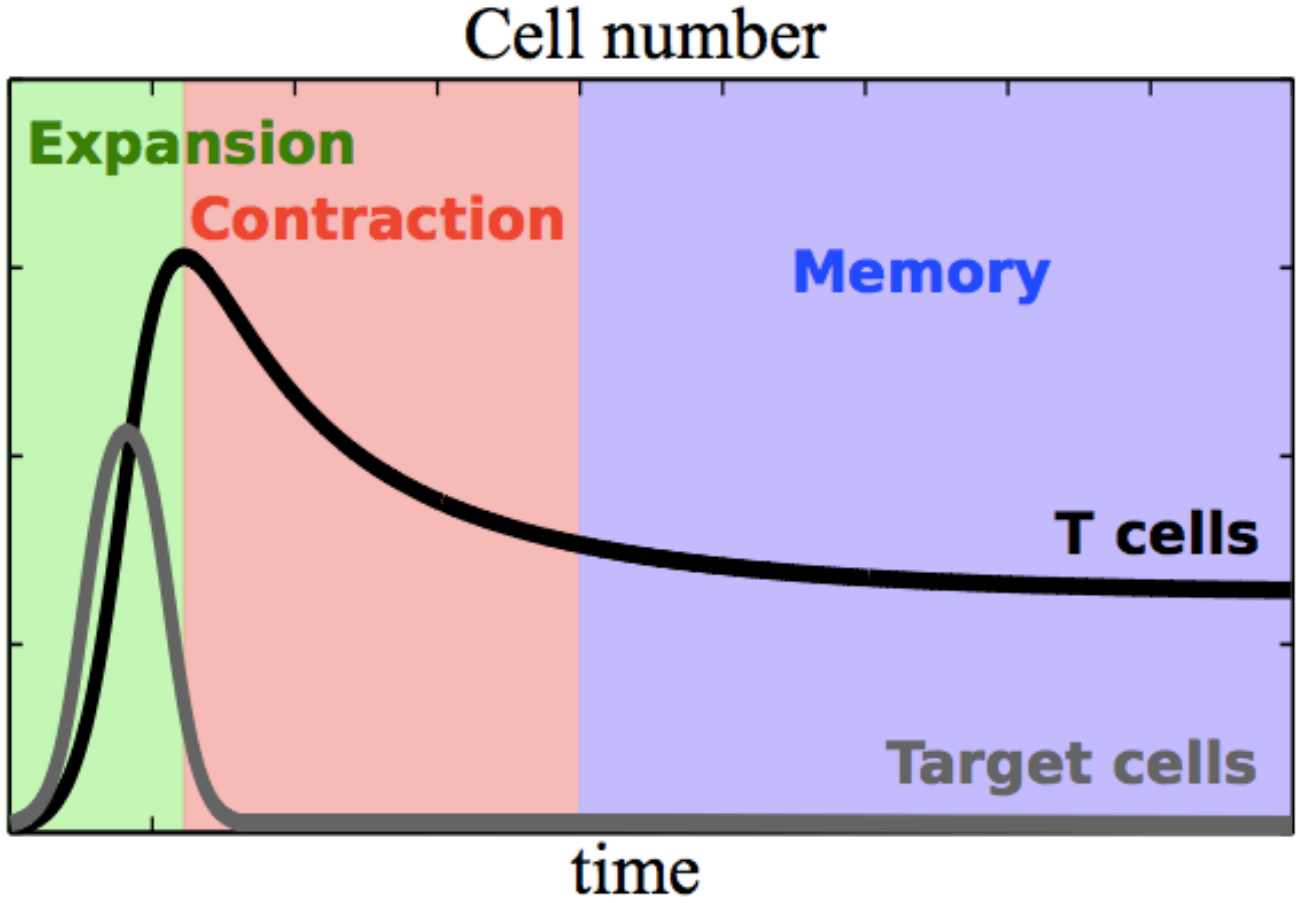
Immunotherapy: boosters of proliferation and immune memory



Evolution of $\varrho_C(T)$ (left panel), $\varrho_I(T)$ (right panel) at the final observation time for different types of boosters: boosters of immune memory (blue dots), boosters of T-cells proliferation (red dots) and combination of boosters of memory and proliferation (green dots) for increasing values of the delivery dose.

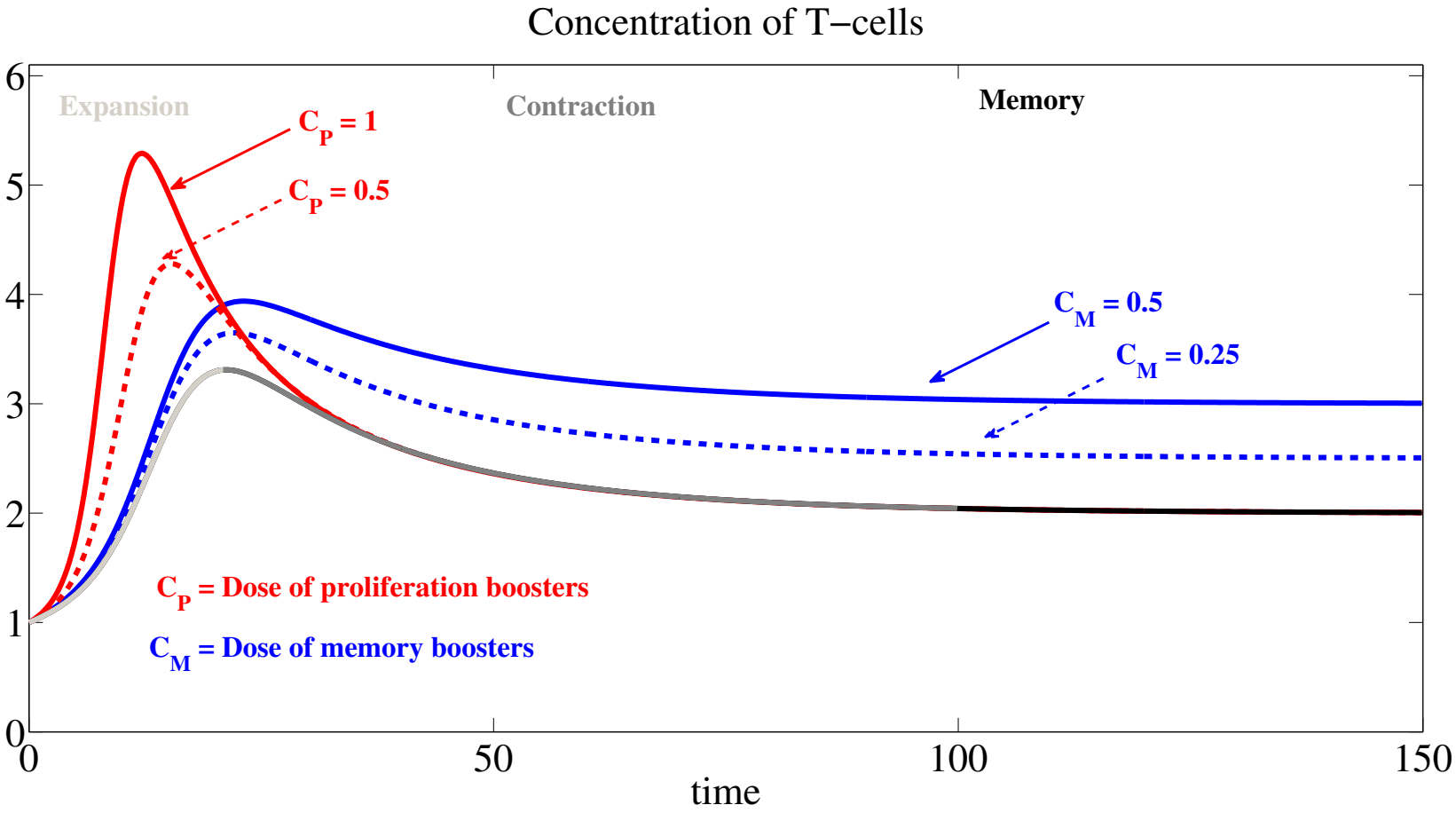
Time phases of the immune response

Expansion, contraction and memory in the immune response with constant immunotherapy. See e.g. *Kaech et alii, Nature Reviews Immunology, 2002.*



T. Lorenzi, R. H. Chisholm, A. Lorz, M. Melensi, M. Delitala. Mathematical model reveals how regulating the three phases of T-cell response can counteract immune evasion, preprint.

Time phases of the immune response



Design **therapeutic interventions** to:

- **Increase** the number of antigen-specific T cells by acting on the **expansion phase**;
- **shorten the duration of the contraction phase** to limit T-cell death and stabilize as many T cells as possible inside the long-lived **memory reservoir**.

Some perspectives

- **Design different immunotherapy protocols** taking into account the time phases of the immune response.
- **Sensitivity analysis** and how some parameters of the model can affect the dynamics of the solution.
- **Parametrize the model** and development of ad-hoc experiments designed to assign precise values to the model parameters and test with some clinical terapeutical protocols.
- **Space dynamics**, cell motility and dynamic evolutionary landscapes.

Concluding remarks

- The proposed **modeling approach** makes possible to take into account proliferation and competition phenomena involving tumor cells as well as tumor-immune interactions and the action of therapeutical agents.
- **Simulations**, developed with an **exploratory aim**, have been addressed to provide insights into the phenomena that rule immune response and therapeutical agents against cancer cells.
- It has been highlighted how the **evolutionary dynamics viewpoint** may give a **further insight** in the dynamic of the system and eventually allow to obtain counter-intuitive results, e.g. immune system may both antagonize and enhance tumor development and progression.