The multi-level view to investigate the cancer progression

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One of the most challenging problem in systems biology is to build a mathematical model able to reproduce a detailed biological systems. To have a functional model generating new hypothesis, one starts by describing the structure of the model (i.e. biochemical reactions or entity interactions), then defines the parameters (i.e. concentrations and reaction rates) to obtain temporal behaviors of these entities. A less explored dimension is the integration of different levels of detail generating a multi-level model able to represent a more realistic and predictive description of cancer.

In this work we investigated the effects of vaccination on a cancer hierarchical structure through a multi-level model [1]. In particular, we propose a new approach which exploits specific interdependencies among population and molecular levels. The overall organization of the method consists of four main steps. (i) *Model definition*, the population level is modeled by a system of Ordinary Differential Equations (ODE) describing the progression of malignant tumors, assuming the validity the cancer stem cells theory [3]. Instead, the molecular level is modeled using the Petri Net (PN) formalism [2] to detail part of the proliferation pathway. (ii) *Model consistency and correctness*, we take advantage from the structural proprieties of PN formalism in order to check if the mass conservation laws are respected. Moreover, we use the model checking techniques to verify if well-known proprieties of the model are modeled in the correct way.(iii) *Multi-level model interactions*, to link populations proliferation parameters with regulation events we identify for each level a set of interaction points, i.e protein playing a pivotal role in proliferation (molecular level) and proliferation rate (population level). (iv) *Model dynamics*, we derive a set of ODEs from the PN model and we analyzed the temporal dynamics of the proteins which play a critical role in cell proliferation through numerical integration. Hence, the obtained quantities are used as parameters in the ODE system modeling the cell proliferation, and it is solved by numerical integration.

In this work we proposed a multi-level approach in which molecular networks are used to estimate parameters of population level. Using this method we have been able to reproduce at a qualitative level the effect of anti-ErbB2 chronic vaccination in BALB-neuT model.

References

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