VBL (Virtual Biophysics Laboratory), the biophysics of tumors and more

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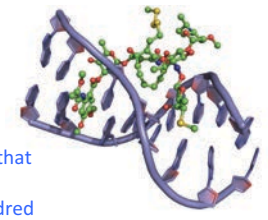
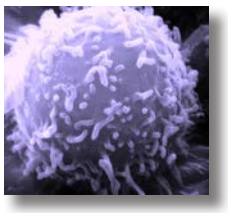
WWW: http://vbl.ts.infn.it/SiteVBL/index.html

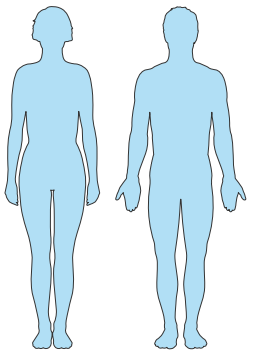
The basic question is: can we link the micro- and the macro-level in biological systems? Can we join all the pieces in a single, comprehensive mathematical model with space- and time-scales that span several orders of magnitude to understand and fight diseases?



A computation that describes molecular behavior – such as that involved in drug action – can require as many as a few hundred million atoms.
To closely follow the dynamics, timesteps must be of the order of picoseconds or less.



An individual cell such as this lymphocyte comprises about 10^{14} atoms, about a million times as large as the largest computations involving single molecules.
Diffusion times can be as short as microseconds, and single processes can last several hours.



The human body contains about 10^{13}-10^{14} cells.
We need to follow the time course of a disease from days to years.

At the very start there are two basic options: analytical or numerical modeling. But analytical modeling requires often shaky and rough approximations, and is not able to incorporate the multitude of local irregularities and statistical fluctuations. These irregularities and fluctuations are specially important in biological systems where they can be amplified by cell proliferation.

On the other hand, numerical work at the most fundamental level, that of individual atoms and molecules, is not feasible. In our own research we have chosen to implement a description at the cellular level. This approach builds on phenomenological descriptions of molecular pathways and of the cell biomechanics, and – while still computationally heavy – it is possible to apply it to describe millions of cells and tissues as large as a few mm.

It must be noted that tumor cells are in a way "simpler" than normal cells, because some of their cellular mechanisms are broken. We simulate clusters of tumor cells in different contexts.

How do we translate biochemical and biophysical processes into equations?

For example, here is how the equations that regulate reaction-diffusion processes in the network of interconnected extracellular spaces and cells look like:

$$\frac{dm_C}{dt} = M(m_C) + T(m_c, m_C)$$

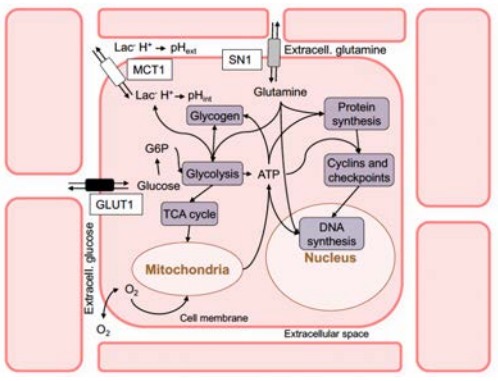
Metabolism (M) and facilitated diffusion(T) into and out of cell. The M and T terms have specific forms for different substances.

$$\frac{dm_c}{dt} = -T(m_c, m_C) + D\sum_{\langle b \rangle}\left(\frac{m_b}{V_b} - \frac{m_c}{V_c}\right)g_{bc} + D_{env}(\rho_{env} - \rho_c)g_c$$

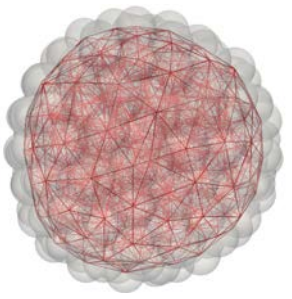
Facilitated diffusion(T) and diffusion in extracellular space

$$\frac{d\rho_{env}}{dt} = -\frac{D_{env}}{V_{env}}\sum_{\langle C \rangle}\left(\rho_{env} - \frac{m_c}{V_c}\right)g_c + (\rho_{in} - \rho_{env})\frac{f}{V_{env}}$$

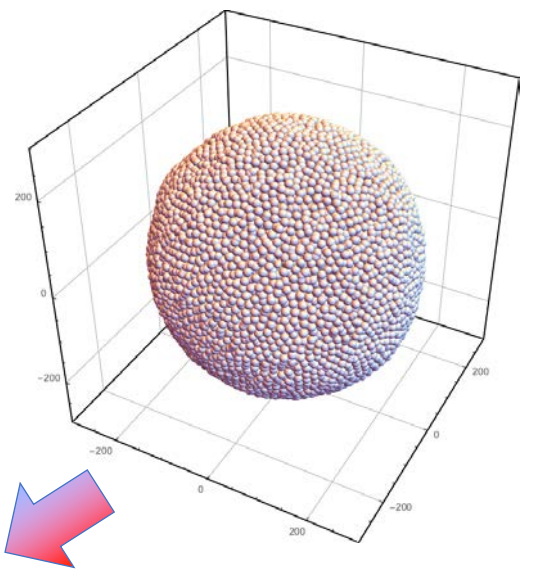
Mass exchange with the environment and bioreactor modeling



We start from a model of individual cells, and their interactions with neighboring cells.

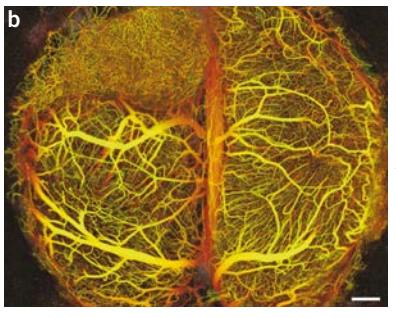


We find the whole network of cell-cell interactions and compute diffusion of nutrients and oxygen in the network, and the biomechanical interactions among cells.

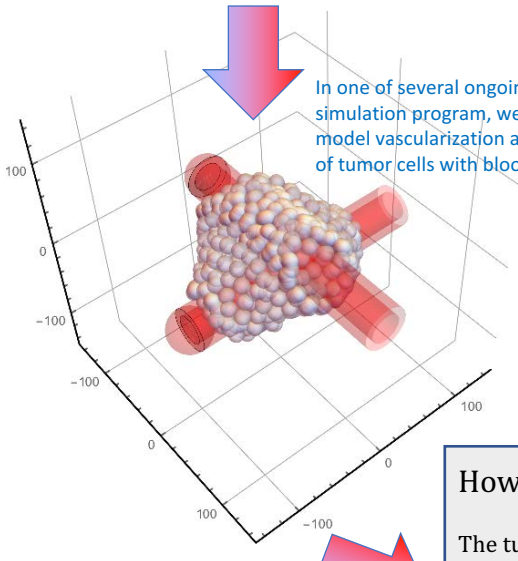


Long runs yield comparatively large structures. These synthetic tumor spheroids can be compared with real spheroids grown *in vitro*.

Image from Yu et al.: "Holographic optical coherence imaging of rat osteogenic sarcoma tumor spheroids", Appl. Optics **43** (2004) 4862



Solid tumors are far more complex than avascular tumor spheroids (the figure shows the depth-projected vasculature within the first 2 mm of mouse brain bearing a xenotransplanted U87 human glioblastoma multiforme tumor imaged with OFDI (Optical Frequency Domain Imaging), scale bar 500 µm, from Vakoc et al. Nature Medicine **15** (2009) 1219), and the the inclusion of vasculature would be one big step towards a realistic model of solid tumors *in vivo*.



In one of several ongoing upgrades of the simulation program, we are starting to model vascularization and the interactions of tumor cells with blood vessels.

How can this be useful?

The tumor microenviroment is often very acidic and hypoxic, and this hinders radiotherapy and chemotherapy of cancer. By understanding the mechanisms of formation of the microenvironment we hope to contribute to improve radio- and chemotherapeutic strategies.

Open problems and challenges

Here is a short and very partial list:

- implementation of important molecular pathways like those that regulate cell acidification
- mathematical description of normal cells and of their interaction with tumor cells
- mathematical definition of different cellular lines
- improved description of cell-cell forces and in general of cell biomechanics
- interaction of cell biomechanics with the molecular environment
- development of evolutionary dynamics in the tumor microenvironment
- simulation of a small solid tumor (1 cm) with vascularization
- simulation of the tumor microenvironment in a solid tumor with vascularization
- ...

Additional information and contacts

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For more information on MSc theses and PhD projects please contact Prof. Edoardo Milotti (room 228, e-mail: edoardo.milotti@ts.infn.it)