In response to ideas coming from Bill Wilson's team, I am starting to explore the feasibility of incorporating something of the agent-based formulation that we're developing for radiation therapy (and drug/radiation therapy) into greensTD.  The radiation model, which we are hoping to estimate parameters for using Cho's experimental results, accounts for repair and misrepair occurring in different ways at the phases of the cell cycle.  Needless to say, we will not be able to include cell division, but we still might be able to learn something from short simulations.

I have just started to think about the task, so this is very preliminary.  My initial thought is that a cell could be associated with each tissue point.  With the current cremaster network.dat (295 segments) there are 78,256 tissue pts, with volume 15x15x15 = 3375 um^3.  That is probably a bit big for a cell, which might have a volume closer to 2000 um^3 - i.e. 12.6x12.6x12.6, giving 130,587 tissue points.  The number of cells would be somewhere in that range.

I think the concentrations of the various constituents at each tissue point will be readily available, and in the simplest case of a radiation dose it will be possible to simulate each cell's passage through the cell cycle and damage, repair and misrepair.  Cells will have to be arrested at mitosis.  The situation becomes more interesting when we are simulating a drug that is being metabolised.  In this case it becomes necessary to simulate the transformation of the drug into its metabolites, which might give rise to bystander effects.  How feasible will it be to account for this transformation in the model?  Effectively each tissue point will become both a sink and a source, with mass flows constantly changing.

(Tim)

Thanks for your message. This sounds like an interesting application of GreensTD. The program is set up to handle situations where solutes react to form other solutes. This is coded in the file tissrate.cpp.dat, which is included in tissrate.cpp when it runs. The example in github shows this:  
  
for(isp=1; isp<=nsp; isp++){    //solute with first-order decay  
        if(isp == 1){  
            mtiss[isp] = tissparam[1][1]\*c[2] - tissparam[2][1]\*c[1];  
            mptiss[isp] = -tissparam[2][1];  
        }  
        else if(isp == 2){            //solute produced by solute 1, with first order decay   
            mtiss[isp] = tissparam[1][2]\*c[1] - tissparam[2][2]\*c[2];  
            mptiss[isp] = -tissparam[2][2];  
        }  
        else printf("\*\*\* Error: Solute not found in tissrate.cpp.dat\n");  
    }  
  
In this example, there is a reversible reaction between solutes 1 and 2, with linear degradation of both solutes. Here mtiss[isp] gives the production rate of solute isp and mptiss[isp] gives the partial derivative of the rate with respect to solute concentration c[isp].  
  
It would also be possible to incorporate variables describing cell state in GreensTD. Such variables would be represented as non-diffusible "solutes" and their rates of change would also be coded in tissrate.cpp.dat. This would be applicable if the model for cell state is deterministic, but not for stochastic models.  
  
I hope that this is helpful.

(Kevin)

Hi Gib, sorry for the slow reply, again!

I really appreciate you and Tim working on this.

My understanding is that the distinction between intracellular and extracellular concentrations is handled in a very similar way in the ABM, Green’s model and Tim’s multilayer fitting program. Basically diffusion occurs by the extracellular route with exchange between IC and EC at each grid point. The Greens and Multilayer fitting programs can have in intracellular diffusion coefficient but we have never used that mainly because I don’t really know what that means – whether diffusivity should be the same but driven by partitioning into cells or the intracellular diffusivity should be different. I guess it depends on the individual situation of application.

I don’t quite understand what you mean by the intracellular and extracellular distinction will disappear in this particular application. In the applications we do solute 1 could be extracellular and solute 2 intracellular or the reaction may be extracellular. Generally we would have a minimum of 4 solutes – 2 extracellular and 2 intracellular with reaction to the other solute in each compartment and exchange between IC and EC for each ie solute 1 and 2 = compound A IC and EC, and solute 3 and 4 = compound 2 IC and EC.

Basically the Greens model can incorporate any PK or PD model that can be formulated as a chemical reaction. I think this is true for the ABM as well but it needs to be coded by you because there is no analogous tissrate.cpp user defined functions.