Multidimensional Monte Carlo Cell Population Dynamics in Virus Replication Systems

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Motivation

Influenza virus infection poses an increasingly serious, maybe even deadly, human health risk. As globalization goes on and virus spread cannot be controlled in reliable ways the risk of infection increases every year. Mutation of new virus types may lead to more dangerous and easy spreading types with epidemic or even pandemic scenarios. Preventing the influenza virus infection by yearly immunization is common practice in many countries all over the world, but global immunization will need vaccines for billions. Today there are well-known limitations on the production, especially when based on egg replication. The development of alternative production methods based on mammalian cell population cultivation and virus replication inside these cells is important to overcome current vaccine production limitations. The optimization of the cell population-based virus replication can be successful accompanied by modelling and simulation.

Process Basics

Mammalian cells (Madin-Darby canine kidney – MDCK) are precultivated in roller bottles, transferred into a bioreactor and grown as adherent cells on microcarriers. They are infected by influenza virus and start replicating virus inside and release it to the medium. After certain time all cells degrade and the process ends. Now all virus is harvested from the medium by several separation steps [1].

Model Formulation and Simulation Details

- Each cell is simulated separately with internal properties based on the virus replication cycle [2] (i=1–N)
- Virus replication is based on the dynamical evolution of three main units inside every cell i:
  - viral genomic RNA (vRNA) \( M_{vRNA} \)
  - viral messenger RNA (vmRNA) \( M_{vmRNA} \)
  - viral complementary RNA (cRNA) \( M_{cRNA} \)
- Replication of cRNA depends on the presence of vRNA and on the variable replication probability \( p_{vRNA} \)
- Replication of vmRNA depends on the presence of vRNA and on the variable transcription probability \( p_{vmRNA} \)
- Replication of vRNA depends on the presence of cRNA and on the variable transcription probability \( p_{cRNA} \)
- Increase or decrease of every unit number inside cell i is carried out at time step \( k \) with a constant cell variation of \( p_{var} = 0.5 \):
  1. Replication of vRNA:
     \[ M_{vRNA}(k+1) = M_{vRNA}(k) + p_{vRNA} \cdot M_{cRNA}(k) \]
  2. Replication of vmRNA:
     \[ M_{vmRNA}(k+1) = M_{vmRNA}(k) + p_{vmRNA} \cdot M_{vRNA}(k) \]
  3. Replication of cRNA:
     \[ M_{cRNA}(k+1) = M_{cRNA}(k) + p_{cRNA} \cdot M_{vmRNA}(k) \]
- Change of virus number in solution \( N_{vir} \) when release threshold \( N_{release} \) is reached for \( M_{vRNA} \) of a cell i with random variation \( r \):
  4a. Virus release:
     \[ N_{vir}(k+1) = N_{vir}(k+1) + ceil(r \cdot M_{vRNA}(k+1)) \]
  4b. Unit decrease:
     \[ M_{vRNA}(k+1) = M_{vRNA}(k) - ceil(r \cdot M_{vRNA}(k)) \]
- Change of unit number \( M_{vmRNA}(k) \) and \( M_{cRNA}(k) \) in each cell i by degradation probability \( p_{deg} \) with random variations \( r' \) and \( r'' \):
  5a. Unit decrease:
     \[ M_{vmRNA}(k+1) = M_{vmRNA}(k) - ceil(r' \cdot M_{vmRNA}(k)) \]
  5b. Unit decrease:
     \[ M_{cRNA}(k+1) = M_{cRNA}(k) - ceil(r'' \cdot M_{cRNA}(k)) \]
- Model implementation in Matlab:
  - Statistical analysis with mean and errors by repeated simulation runs (approx. \( m = 1 \rightarrow 20 \))
  - Use of different random number generators to avoid inherent systematics (twister, combRecursive, multiFibonacci)
  - Variation of total cell numbers for finite size analysis (\( N = 100 \rightarrow 100.000 \))

Experiment vs. Simulation

Experimental data from hemagglutination assay (HA, [3]), fluorescence microscopy units (FU, [4]) and quantitative real time reverse transcriptase polymerase chain reaction assay (RT-qPCR, [3]). Simulation results of average data for the virus number in solution (compare to HA, left-top), of distributed data of average molecule numbers inside the whole cell population (compare to FU, left-bottom) and of averaged data of selected molecule units inside cells from the complete cell population (compare to RT-qPCR, middle), as well as distributions of molecule unit numbers from the cell population (right).