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Investigating Candida albicans resistance in whole-blood assays by virtual infection models using parallelized parameter estimation

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Investigating *Candida albicans* resistance in whole-blood assays by virtual infection models using parallelized parameter estimation

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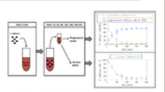
1. Human Whole-Blood Infection Assay

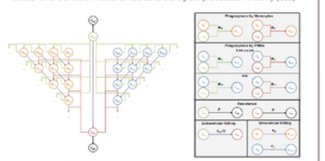
- *C. albicans*: an opportunistic fungal pathogen in humans
- acquisition of time resolved data with the help of infection assay [1]
- quantification of non-spatial properties concerning the immune response [1,2]



Whole-Blood Assay and Data Collection [1]

2. State-Based Virtual Infection Model

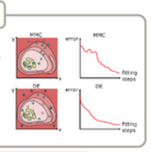
- modeling of biological processes observed in experiments
- states and transition rates to recreate biological processes virtually [1,2]



Flow Diagram and Transition Rates between States [1]

3. Fitting Algorithms

- fitting of estimations to data with fitting algorithms and error function
- various fitting algorithms
- in-depth testing of local and global algorithms
- Metropolis Monte Carlo (MMC) and Differential Evolution (DE) with most promising results



4. Modification and Parallelization

- unknown process of resistance acquisition by *C. albicans* cells against phagocytosis and killing by immune cells
- testing whether a humoral distribution of proteins could be the reason

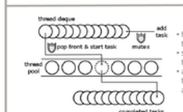
Modified Rates:

Spontaneous Resistance Acquisition Rate:

$$p = constant$$

PMN-Mediated Resistance Acquisition Rate:

$$\rho(t = n\Delta t) = \tilde{p} \sum_{m=0}^{n} \frac{N(t = m\Delta t)}{G_{(0,0)}} \cdot \exp(-\gamma_d \Delta t(n - m))$$



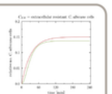
- fitting runs as tasks in a thread deque
- simultaneous execution of n tasks by thread pool object
- after completion of a new task the deque will start automatically

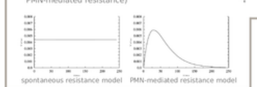
Advantages of Thread Pools:
no waiting time no manual starts gain of function

5. Results and Comparison

Modification

- suitable parameter estimations
- spontaneous resistance mechanism shows larger time window for resistance acquisition (see below)
- different models indicate minor differences (see right figure, red for spontaneous, green for PMN-mediated resistance)

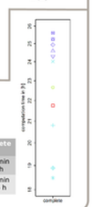




spontaneous resistance model PMN-mediated resistance model

Parallelization

- decrease from 7 days to 22 hours when using MMC (see red square on the right)
- time saving of about 87%



	650 cells	6500 cells	65000 cells	650000 cells	complete
serial	2100 min 35 h	3180 min 53 h	1860 min 31 h	2700 min 45 h	9840 min 164 h
parallel	56.5 min 0.94 h	97.5 min 1.62 h	290 min 4.83 h	861 min 14.35 h	1305 min 21.75 h

6. Discussion

- results show possibility of a PMN-mediated resistance acquisition
- no experimental data to distinguish between resistance mechanisms
- significant decrease of computation time

References
[1] Hünniger and Lehnert et al., PLOS Comp Biol. (2014)
[2] Lehnert and Timme et al., Frontiers in Microbiology (2015)

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