Effects of stochasticity in models of the cell cycle: from quantized cycle times to noise-induced oscillations

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Math models of the cell cycle

- Increasing knowledge about molecular components
- At core of models are cyclin-dependent kinases (CDKs) and their cyclin proteins
  - Regulate progression through cell cycle
- Introduce stochasticity
  - Aim at the molecular level
ODE model vs. Stochastic differential equation model

- **Ordinary differential equation (ODE) model**
  - Deterministic
    - Initial conditions
    - Everything is predefined

- **Stochastic model**
  - Introduce inherent fluctuations, or noise
  - Use random numbers
    - Vary between simulations
Purpose of including stochasticity

- Better agreement with experimental finding
  - Quantized cycle lengths in the $\text{wee1-cdc25}\Delta$ mutant of fission yeast

- Qualitatively different behavior
  - Noise can serve as a control
  - May work to system’s advantage
Focus on M-phase promoting factor (MPF)

- Protein complex that triggers a cell to enter the M phase
- Has two subunits
  - Cdc2 (catalytic subunit)
  - Cdc13 (regulatory subunit)
- Regulated by proteolysis of Cdc13, phosphorylation of Cdc2, and stoichiometric inhibition (Rum1)
\[
\frac{d[Cdc13_{1}]}{dt} = k_1 M - (k'_2 + k''_2 [Ste9] + k''_2 [Slp1]) [Cdc13_{1}]
\]
\[
\frac{d[preMPF]}{dt} = k_{wee}[Cdc13_{1}] - [preMPF] - k_{24}[preMPF]
\]
\[
\frac{d[Ste9]}{dt} = (k'_3 + k''_3 [Slp1]) \frac{1}{J_3 + 1} - [Ste9]
\]
\[
- (k'_4 [SK] + k_4 [MPF]) \frac{[Ste9]}{J_4 + [Ste9]}
\]
\[
\frac{d[Slp1_{1}]}{dt} = k'_5 + k''_5 \frac{[MPF]^4}{J_5 + [MPF]^4} - k_6 [Slp1_{1}]
\]
\[
\frac{d[Slp1]}{dt} = k_7 [IEP] \frac{[Slp1_{1}] - [Slp1]}{J_7 + [Slp1_{1}] + [Slp1]} - k_8 \frac{[Slp1]}{J_8 + [Slp1]} - k_6 [Slp1]
\]
\[
\frac{d[IEP]}{dt} = \frac{k_9 [MPF]}{J_9 + [IEP]} - k_{10} [IEP]
\]
\[
\frac{d[Rum1_{1}]}{dt} = k_{11} - (k_{13} + k'_{12} [SK] + k''_{12} [MPF]) [Rum1_{1}]
\]
\[
\frac{d[SK]}{dt} = k_{13} [TF] - k_{14} [SK]
\]
\[
\frac{dM}{dt} = \mu M
\]

Cell mass is divided by two, when [MPF] crosses 0.1 from above (end of mitosis).

\[
\Sigma + \sqrt{\Sigma^2 - 4[Cdc13_{1}][Rum1_{1}]}
\]

\[
[MPF] = \frac{2[Cdc13_{1}][Rum1_{1}]}{[Cdc13_{1}] - [preMPF]([Cdc13_{1}] - [Trimer])}
\]

\[
[TF] = GK(k_{15} M, k'_{16} + k''_{16} [MPF], J_{15}, J_{16})
\]

with:

\[
k_{wee} = k'_{wee} + (k''_{wee} - k''_{wee}) GK(V_{awee}, V_{awee} [MPF], J_{awee}, J_{wee})
\]

\[
k_{25} = k'_{25} + (k''_{25} - k''_{25}) GK(V_{aw}, V_{aw} [MPF], J_{aw}, J_{25})
\]

\[
\Sigma = [Cdc13_{1}] + [Rum1_{1}] + K_{dis}
\]

\[
GK(a, b, c, d) = \frac{2ad}{b - a + bc + ad + \sqrt{(b - a + bc + ad)^2 - 4ad(b - a)}}
\]

\[
k_1 = 0.03, k'_2 = 0.03, k''_2 = 1.0, k''_2 = 0.1
\]

\[
k' = 1.0, k'' = 10.0, J_3 = 0.01
\]

\[
k'_4 = 2.0, k_4 = 35.0, J_4 = 0.01
\]

\[
k'_5 = 0.005, k''_5 = 0.3, J_5 = 0.3, k_6 = 0.1
\]

\[
k_7 = 1.0, k_8 = 0.25, J_7 = J_8 = 0.001
\]

\[
k_9 = 0.1, k_{10} = 0.04, J_9 = J_{10} = 0.01
\]

\[
k_{11} = 0.1, k_{12} = 0.01, k'_{12} = 1, k''_{12} = 3
\]

\[
k_{13} = 0.1, k_{14} = 0.1
\]

\[
\mu = 0.005 \text{ (mass growth rate)}
\]
Converting ODE model into a stochastic model

- No specific knowledge about the nature of the stochastic fluctuations
  - General description of the inclusion of stochasticity
- Rewritten as Langevin-type equations with multiplicative noise
- For a single species \( x_i \)

\[
\frac{dx_i}{dt} = f_i[...] + g(x_i) \xi_i(t)
\]
Derivation of $g(x)$

- Assumed that the relative fluctuations scale as the inverse square root of the concentration:

$$\frac{g(x_i)}{x_i} \frac{1}{\sqrt{x_i}} \rightarrow g(x_i) = \sqrt{2D_i x_i}$$

- $D$, a constant for noise amplitude is made constant for simplicity
- $D$ is made small
  - Original dynamics assumed to be accurate
- Generic for stochastic processes
Deterministic vs. stochastic simulation
Comparison with experimental data

- Negative correlation is an indicator of size control
**wee1-cdc25Δ double mutant: the existence of quantized cycle lengths**

- If these proteins are absent, positive feedback loops driving cell into mitosis are weak.
- MPF cannot increase abruptly at onset of mitosis.
- Negative feedback loop drives cell back into G2.
- Mass will be larger when cell prepares again for mitosis.
Experimental data vs. the deterministic model

- Experimental data shows 3 or 4 characteristic clusters in the CT vs. mass-at-birth plot
- Deterministic model: periodically alternating long and short CTs
  - CT exclusively determined by cell mass at birth
  - Does not account for characteristic clustering
Comparison of stochastic and deterministic model results
Checkpoint mechanisms vs. limit cycles

- External and internal factors either ensure stability of steady state or state loses stability and goes to next checkpoint.

- If cell size kept at constant below the G2-M size requirement:
  - Deterministic model: cell cycle progress is halted.
  - Stochastic model: interrupted by large outbreaks of MPF activity, producing coherent oscillations.
Simplified model of the division control system

- Point: to investigate why with noise oscillations occur when cell size is kept constant
- Division control system can be approximated by 2 differential equations:

\[
\begin{align*}
\frac{du}{dt} &= \frac{k_1'}{G} - [k_2(u) + k_{wee}]u + k_{25}(u)\left(\frac{v}{G} - u\right) \\
&\quad + g(u)\xi(t), \\
\frac{dv}{dt} &= k_1' - k_2(u)v
\end{align*}
\]

- \(u\) is the relative MPF concentration, \(v\) is the relative cyclin concentration, \(g(u)\) is an additional noise term.
Noise-induced oscillations

- Parameters made such that there is a stable steady state with low MPF activity (G2-arrested cells)
- Deterministic model stays arrested in G2
  - In actuality, somatic cells still divide
- Introduction of noise: small perturbations of steady state can induce large activations of MPF
  - Similar to what happens for wild type fission yeast
Noise-induced oscillations

- Without noise, model will stay at steady state
- Findings suggest there might be regulatory mechanisms preventing noise-induced outbreaks of MPF activity
Noise is not necessarily a nuisance

- Noise amplitude acts like a bifurcation parameter
- Regulatory system is controlled by varying noise amplitude
Conclusion

- The inclusion of noise is in good agreement with experimental findings.
- Even small amounts of noise may result in outbreaks of MPF activity.
  - The exact mechanism by which cell size regulates the progression through the cell cycle is not known.
- Noise and fluctuations might play a more vital role in cell regulations than previously thought.
How this relates to my work

- Conversion of a deterministic model into a stochastic model
- Nuclear factor κB (NF-κB)
  - Transcription factor important in regulating numerous genes important for things including the immune response
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