Intrinsic Fluctuations in the Brusselator Model: Metastability and Switching

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THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. University of Manchester

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Theoretical Motivation

In a chemical reaction system, diffusion can be a destabilizing influence leading to oscillations, waves and spatial patterns.
Problem: Patterns are often only observed when the parameters are fine tuned

Problem: Diffusion coefficients of different chemical species must differ by a large amount

Solution? We must consider fluctuations intrinsic to the system: Demographic noise / Intrinsic Fluctuations
• At the microscopic level, discrete entities are undergoing reactions and diffusion.

• Coarse-grained (Mean-field) rate equation descriptions become suspect either when
  • # of reactants is small or
  • diffusion is slow compared to reaction rates and the characteristic volume, $V$, is small
  • OR the meanfield equations admit a line of fixed points
- Intrinsic fluctuations give rise to bistability not present in mean-field model
- Mean-field behavior is recovered in large $N$ limit
Example: *Intrinsic* Fluctuations in Predator-Prey Dynamics

\[ \dot{u} = p_2 uv - du \]
\[ \dot{v} = bv - cv^2 - p_1 uv \]

- \( B \rightarrow 2B \)
- \( B \rightarrow 0 \)
- \( A + B \rightarrow A \)
- \( A + B \rightarrow 2A \)
- \( A \rightarrow 0 \)
Predator-Prey Model With Diffusion

Butler and Goldenfeld, Phys. Rev. E 80, 030902(2009)

- Intrinsic fluctuations allow for pattern formation outside region predicted by standard Turing analysis
- Effect of noise persists in the thermodynamic limit!
Increased Coupling Dead state

Experimental Motivation: Belousov-Zhabotinsky (BZ)

A Model of Chemical Oscillations

The Brusselator

\[ \begin{align*}
0 & \rightarrow \quad X : N \\
X & \rightarrow \quad Y : bn_x \\
2X + Y & \rightarrow \quad 3X : cn_x^2 n_y / N^2 \\
X & \rightarrow \quad 0 : n_x
\end{align*} \]

Mean-Field Rate Equations

\[ \begin{align*}
\dot{x} &= 1 - (b + 1)x + cx^2y \\
\dot{y} &= bx - cx^2y
\end{align*} \]

Unique Fixed Point: \( (x^*, y^*) = (1, b/c) \)

Stability Conditions: \( b < c + 1 \)

Brusselator phase diagram from linear stability analysis
The well mixed Brusselator (Point Oscillator)

Mean-Field Rate Equations

\[
\begin{align*}
\dot{x} &= 1 - (b + 1) x + cx^2 y \\
\dot{y} &= bx - cx^2 y
\end{align*}
\]

Phase Diagram

Stable Fixed Point

Limit Cycle
The well mixed Brusselator (Point Oscillator)

Mean-Field Rate Equations
\[ \dot{x} = 1 - (b + 1)x + cx^2y \]
\[ \dot{y} = bx - cx^2y \]

Phase Diagram

Stable Fixed Point

Limit Cycle
Timescale Separation: Mean-Field

- $c \ll 1$
- $c = 1$
- $c \gg 1$

$C = c \Delta t$

$c$ sets the ratio of activator to inhibitor timescales.

Amplitude $c = 9.0$.

1.0

0.2 0.0 0.2 0.4 0.6

$\delta$
The Brusselator With Intrinsic Fluctuations
\[ \dot{P}_n(t) = \sum_{n' \neq n} \left( T(n|n') P_{n'} - T(n'|n) P_n \right) \]

**Master Equation**

**Random Walk Picture**

**The Brusselator**

\[
\begin{align*}
0 & \rightarrow X : N \\
X & \rightarrow Y : b_n x \\
2X + Y & \rightarrow 3X : c_n^2 n_y / N^2 \\
X & \rightarrow 0 : n_x
\end{align*}
\]
Master Equation

\[ \dot{P}_n(t) = \sum_{n' \neq n} \left( T(n|n')P_{n'} - T(n'|n)P_n \right) \]

Random Walk Picture

The Brusselator

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Species</th>
<th>Rate Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 \rightarrow X</td>
<td>X</td>
<td>N</td>
</tr>
<tr>
<td>X \rightarrow Y</td>
<td>Y</td>
<td>bn_x</td>
</tr>
<tr>
<td>2X + Y \rightarrow 3X</td>
<td>X, Y</td>
<td>cn_x^2 n_y/N^2</td>
</tr>
<tr>
<td>X \rightarrow 0</td>
<td>X</td>
<td>n_x</td>
</tr>
</tbody>
</table>
\[ \dot{P}_n(t) = \sum_{n' \neq n} \left( T(n|n')P_{n'} - T(n'|n)P_n \right) \]
Master Equation - Small Fluctuation Expansion

\[ \dot{P}_n(t) = \sum_{n' \neq n} \left( T(n|n') P_{n'} - T(n'|n) P_n \right) \]

\[ \frac{n}{N} = \mathbf{x}(t) + N^{-1/2} \xi \]

**Average concentration**

**Fluctuations about the average**

**Leading Order:**

\[ \dot{x} = 1 - (b + 1) x + c x^2 y \]

\[ \dot{y} = bx - cx^2 y \]

**Next Leading Order:**

\[ \frac{\partial}{\partial t} \Pi(\vec{\xi}, t) = - \sum_{i,j} K_{ij}(t) \frac{\partial}{\partial \xi_i} (\xi_j \Pi(\vec{\xi}, t)) + \sum D_{ij}(t) \frac{\partial}{\partial \xi_i} \frac{\partial}{\partial \xi_j} \Pi(\vec{\xi}, t) \]
Master Equation - Small Fluctuation Expansion

**Linear Fokker-Planck Equation**

\[
\frac{\partial}{\partial t} \Pi(\vec{\xi}, t) = - \sum_{i,j} K_{ij}(t) \frac{\partial}{\partial \xi_i} (\xi_j \Pi(\vec{\xi}, t)) \\
+ \sum D_{ij}(t) \frac{\partial}{\partial \xi_i} \frac{\partial}{\partial \xi_j} \Pi(\vec{\xi}, t)
\]

**Linear Langevin Equation**

\[
\dot{\vec{\xi}} = K \vec{\xi} + \vec{f}(t)
\]

Gaussian white noise

\[
\langle |\xi(\omega)|^2 \rangle = P_x(\omega) = \frac{2((1 + b)\omega^2 + c^2)}{(c - \omega^2)^2 + (1 + c - b)^2\omega^2}
\]
Master Equation: Gillespie Algorithm

\[ c \ll 1 \]

\[ c = 1 \]

\[ c \gg 1 \]

Time Series of \( x(\text{black}) \) and \( y(\text{red}) \)

"Quasi-cycles"

Master Equation: van Kampen Expansion

\[ \dot{P}_n(t) = \sum_{n' \neq n} \left( T(n|n')P_{n'} - T(n'|n)P_n \right) \]

\[ \frac{n}{N} = x(t) + N^{-1/2} \xi \]

Power Spectrum

\[ P_x(\omega) = \frac{2((1 + b)\omega^2 + c^2)}{(c - \omega^2)^2 + (1 + c - b)^2\omega^2} \]

Average concentration

Fluctuations about the average
c sets the ratio of activator to inhibitor timescales

$$c = \frac{\tau_x}{\tau_y}$$
Master Equation: van Kampen Expansion

\[ \dot{P}_n(t) = \sum_{n' \neq n} \left( T(n|n')P_{n'} - T(n'|n)P_n \right) \]

\[ \frac{n}{N} = x(t) + N^{-1/2}\xi \]

Average concentration

Fluctuations about the average

\[ P_x(\omega) = \frac{2((1 + b)\omega^2 + c^2)}{(c - \omega^2)^2 + (1 + c - b)^2\omega^2} \]

Power Spectrum

\[ N = 10^5 \]
Master Equation: van Kampen Expansion

\[ \dot{P}_n(t) = \sum_{n' \neq n} \left( T(n|n') P_{n'} - T(n'|n) P_n \right) \]

\[ \frac{n}{N} = \mathbf{x}(t) + N^{-1/2} \xi \]

Power Spectrum

\[ P_x(\omega) = \frac{2((1 + b)\omega^2 + c^2)}{(c - \omega^2)^2 + (1 + c - b)^2\omega^2} \]
Timescale Separation: Stochastic

\[ c \ll 1 \quad \quad c = 1 \quad \quad c \gg 1 \]

\[ X/N \quad \text{vs} \quad Y/N \]

Time Series of \( x(\text{black}) \) and \( y(\text{red}) \)
Metastable Oscillations: First Passage

\[\begin{align*}
\tau_L & : \text{First passage time from large to small amplitude oscillations} \\
\tau_S & : \text{First passage time from small to large amplitude oscillations}
\end{align*}\]
First Passage Times

**Small to Large**

Scaling Function:

\[ \langle \tau_s \rangle = N^{-\beta_s} f(\delta N^{\alpha_s}) \]

\[ \alpha_s = 0.82 \]

\[ \beta_s = -1.12 \]

**Large to Small**

\[ \langle \tau_L \rangle = N^{-\beta_L} g(\delta N^{\alpha_L}) \]

\[ \alpha_L = 0.2 \]

\[ \beta_L = 0.2 \]
First Passage Times (Finite Thermodynamic Limit)

In the Thermodynamic limit: Oscillations persist contrary to meanfield expectations.
The Future!
Spatially extended Brusselator (1d)

We model the one dimensional system as a lattice of well mixed volumes. Reactants can hop between volumes with specified rates.

Reactions:

- $0 \rightarrow X_i : N$
- $X_i \rightarrow Y_i : bn_x$
- $2X_i + Y_i \rightarrow 3X_i : cn_x^2 n_y/N^2$
- $X_i \rightarrow 0 : n_x$

with hopping:

- $X_i \rightarrow X_{i\pm 1} : D_x$
- $Y_i \rightarrow Y_{i\pm 1} : D_y$
Spatially extended Brusselator (1d)

**Mean-Field:**

\[
\frac{\partial x}{\partial t} = 1 - (1 + b)x + cx^2y + D_x \nabla^2 x
\]

\[
\frac{\partial y}{\partial t} = bx - cx^2y + D_y \nabla^2 y
\]
Spatially extended Brusselator (1d)

Increasing Inhibitor Diffusion
Spatially Structured Lattice (1d)

Reactions:

\[
\begin{align*}
0 & \rightarrow X_i : N \\
X_i & \rightarrow Y_i : bn_x \\
2X_i + Y_i & \rightarrow 3X_i : cn_x n_y / N^2 \\
X_i & \rightarrow 0 : n_x \\
\end{align*}
\]

\{ odd sites only \}

w/ hopping:

\[
\begin{align*}
X_i & \rightarrow X_{i\pm1} : D_x \\
Y_i & \rightarrow Y_{i\pm1} : D_y \\
\end{align*}
\]
**Summary**

- Intrinsic fluctuations can give rise to interesting behavior not accessible in the mean-field limit.
- Fluctuations still play an important role in large systems.
- Line of Fixed Points leads to new deterministic behavior.

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