Stochastic Simulation of Reaction-Diffusion Systems

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Why are we here?

(Some) comms engineers interested in reaction-diffusion systems
### Why are we here?
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### What have we done?
- Applied comms engineering to chemical signalling in fluids
- Developed a reaction-diffusion simulator for comms analysis
### Why are we here?
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### What have we done?
- Applied comms engineering to chemical signalling in fluids
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### Where are we going?
Understand and control communication in “small” natural systems
1 Background

2 The AcCoRD Simulator

3 Recent Feature Development
   Absorbing Surfaces
   Mesoscopic Flow

4 On-Going Work
   Behavioural Dynamics
   Information Transfer

5 Conclusions
What is Communications Engineering?
Designing communication systems and measuring their performance
What are Communication Networks?
From conventional networks to molecular communication
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From conventional networks to molecular communication
Examples of Molecular Communication

Neuromuscular Junction

Presynaptic Cleft (Neuron) 30 nm Postsynaptic Cleft (Muscle)

Neurons control muscle contraction
Examples of Molecular Communication

Neuromuscular Junction

Presynaptic Cleft (Neuron)  Δ  30 nm  Δ  Postsynaptic Cleft (Muscle)

Quorum Sensing

Low Density  Δ  High Density

Bacteria estimate population density

Bacteria control muscle contraction
How Does Engineering Integrate?

Biological Signalling \iff Communications and Signal Processing

Long-Term Question
How to design small systems with living and synthetic devices where we can predict and control behaviour?
Future Applications of Molecular Communication

- Drug delivery
- In vivo diagnostics
- Lab-on-a-chip
- Chemical reactors
- Pollution monitoring
Future Applications of Molecular Communication

Drug delivery
Future Applications of Molecular Communication

Drug delivery

In vivo Diagnostics
Future Applications of Molecular Communication

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In vivo Diagnostics

Lab-on-a-chip
Future Applications of Molecular Communication

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Lab-on-a-chip

Chemical reactors

Pollution monitoring
Molecular Communication Channels are Different

Nodes may be simple, molecules must be physically sent
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Nodes may be simple, molecules must be physically sent
Molecular Communication Experiments

Tabletop Signalling\textsuperscript{1}

\begin{itemize}
\item Krishnaswamy et al., \textit{Proc. IEEE ICC}, Jun. 2013
\end{itemize}
Molecular Communication Experiments

Tabletop Signalling


Molecular Communication Experiments

Tabletop Signalling

Using Bacteria as Transceivers

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Our Contributions to Channel Modelling

“Enhanced” Diffusion

Molecule Degradation

\[ \begin{array}{c}
A & E & k_i & \rightarrow & k_i & \rightarrow & \times & \rightarrow & A_p & E \\
\end{array} \]

With Degradation

Baseline

Simulation of Reaction-Diffusion Systems


Our Contributions to Channel Modelling

“Enhanced” Diffusion

Molecule Degradation

![Diagram of Molecule Degradation](image)

Bulk Fluid Flow

![Diagram of Bulk Fluid Flow](image)

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Our Contributions to Channel Modeling

Point-to-Point Model Accuracy

Our Contributions to Channel Modeling

Point-to-Point Model Accuracy


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Why Simulate Mol Comm Systems?

Generic reasons for simulation:

- Test assumptions
- Verify expected behaviour
  - E.g., Channel response, bit error rate

Specifically for Mol Comm:
- Channels can be very complex
- Physical space
- Many phenomena
- Understand unfamiliar environments
  - We can control/design the channel
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Scales of Molecular Simulations

Simulation of Reaction-Diffusion Systems

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Scales of Molecular Simulations

Simulation of Reaction-Diffusion Systems

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Scales of Molecular Simulations

Simulation of Reaction-Diffusion Systems

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Scales of Molecular Simulations

Simulation of Reaction-Diffusion Systems

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Generic Simulators – Existing platforms from physical chemistry
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Advantages:

- Advanced “sandbox” tools
- Open source and commercial platforms
- Options for all physical scales
- Many are maturely developed

Disadvantages (for molecular communication):

- Not designed for data transmission
- Not designed for channel statistics
- Not always spatially tunable
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COMSOL Multiphysics (Continuum)$^1$

ANSYS (Continuum)$^2$

Images: $^1$https://uk.comsol.com/multiphysics/what-is-mass-transfer
$^2$https://www.ansys.com/products/fluiddynamics
Popular Generic Simulators
Sample Open Source Platforms

URDME (Mesoscopic)$^1$

Smoldyn (Microscopic)$^2$

LAMMPS (Mol. Dynamics)$^3$

Images: $^1$https://doi.org/10.1186/1752-0509-6-76, $^2$https://doi.org/10.1371/journal.pcbi.1000705,
$^3$https://lammps.sandia.gov/prepost.html
Molecular Communication Simulators

Mol Comm Simulators – Developed within MC research community
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Advantages:

- Designed for data transmission
- Designed for channel statistics
- Free if available

Disadvantages:

- Most are not generic solvers
- Implement specific environments
- No options for all scales
- Development focused on microscopic; some mesoscopic
- Not as maturely developed
- Not all readily accessible
Molecular Communication Simulators

**Mol Comm Simulators** – Developed within MC research community

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https://www.youtube.com/watch?v=xOGkKG8PsCE
AcCoRD (Actor-based Communication via Reaction-Diffusion)

- Flexible environmental design ("sandbox")
- Generate many independent realizations
- Release molecules based on modulated data
- Track number or locations of molecules

https://www.youtube.com/watch?v=7QcN6eGrC4w
Sample AcCoRD Results

Molecule Observation Distributions

Mean Behaviour

Simulation of Reaction-Diffusion Systems

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5 Conclusions
• Receivers commonly modelled as absorbing surfaces

• Microscopic simulation - displacements are straight lines
• “Simplistic Monte Carlo” (SMC; Arifler and Arifler, 2017)
• Final point within absorbing object is obvious
Absorbing Surfaces

Absorbing Surfaces

- Need small time steps $\Delta t$ to model path
- Absorption takes LONG time to simulate accurately

Absorbing Surfaces

“Refined Monte Carlo” (RMC; Arifler and Arifler, 2017)

- Assume sphere is flat infinite plane and check absorption probability

\[
Pr_{\text{RMC}} = \exp \left( -\frac{l_i l_f}{D \Delta t} \right)
\]

“A priori Monte Carlo” (APMC)

• Check for absorption BEFORE diffusing

\[ P_{r_{APMC}} = \frac{r_r}{r_0} \text{erfc} \left( \frac{r_0 - r_r}{\sqrt{4D\Delta t}} \right) \]

• More accurate for large time steps and when far from receiver

Absorbing Surfaces

Performance

- Distance $r_0 = 50 \mu m$, receiver radius $r_r = 0.5 \mu m$

Absorbing Surfaces
Performance with Different $\Delta t$

- Distance $r_0 = 50 \mu m$, receiver radius $r_f = 5 \mu m$
• Distance $r_0 = 50 \mu m$, receiver radius $r_r = 5 \mu m$
Absorbing Surfaces
Performance with Different $\Delta t$

- Distance $r_0 = 50 \mu m$, receiver radius $r_f = 5 \mu m$
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- Distance $r_0 = 50 \, \mu m$, receiver radius $r_r = 5 \, \mu m$
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Absorbing Surfaces

Performance with Different $\Delta t$

- Distance $r_0 = 50 \mu m$, receiver radius $r_r = 5 \mu m$
Absorbing Surfaces
Performance with Multiple Receivers (Limited Analytical Results)

- Distance $r_0 = 100 \mu m$, $\Delta t = 0.2$ s

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3 Recent Feature Development
   - Absorbing Surfaces
   - Mesoscopic Flow

4 On-Going Work
   - Behavioural Dynamics
   - Information Transfer

5 Conclusions
Divide fluid environment into **virtual subvolumes** (containers)
- Track number of molecules of each type in each subvolume
- Reaction and diffusion events change molecule counts
Divide fluid environment into virtual subvolumes (containers)

- Track number of molecules of each type in each subvolume
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**Mesoscopic Model**

Divide fluid environment into virtual subvolumes (containers)

- Track *number of molecules of each type* in each subvolume
- Reaction and diffusion events change molecule counts

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### Mesoscopic Model

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Mesoscopic simulations need **rates** to predict when events occur

- Every event has a propensity $\alpha$
  - $\alpha$ depends on the rate $k$, i.e., $\alpha = f(k)$
- For transitions between subvolumes, propensity is $\alpha = kU$
  - $U$ – number of molecules of same type within subvolume

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  - For transitions between subvolumes, propensity is $\alpha = kU$
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Next event time is then

$$t_{\text{next}} = -\frac{\log u}{\alpha}$$

where $u$ is a uniform RV $u \in (0, 1]$

- Different ways to deal with large number of potential events

---

Mesoscopic Rates with Flow

- \( v \) – flow speed perpendicular to subvolume face (assume positive)
- \( D \) – diffusion coefficient
- \( k_w \) – transition rate in direction of flow
- \( k_a \) – transition rate against direction of flow

Diffusion Only \((v = 0)\)

\[
k_a = k_w = \frac{D}{h^2}
\]
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**Diffusion Only ($v = 0$)**

$$k_a = k_w = \frac{D}{h^2}$$

**“Naive” Flow Model**

$$k_w = \frac{D}{h^2} + \frac{v}{h}$$

$$k_a = \frac{D}{h^2}$$

Mesoscopic Rates with Flow

- \( v \) – flow speed perpendicular to subvolume face (assume positive)
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Diffusion Only \((v = 0)\)

\[
\begin{align*}
  k_a &= k_w = \frac{D}{h^2} \\
  k_a &= \frac{D}{h^2}
\end{align*}
\]

"Naive" Flow Model

\[
\begin{align*}
  k_w &= \frac{D}{h^2} + \frac{v}{h} \\
  k_a &= \frac{D}{h^2} - \frac{v}{2h}
\end{align*}
\]

Proposed Flow Model

• Need to make sure transition rates aren’t negative

Mesoscopic Flow Performance

- Subvolume size $h = 1 \mu m$, flow speed $v = 0.1 \text{ mm/s}$

• Subvolume size $h = 1 \mu m$, flow speed $v = 0.1 \text{ mm/s}$

Mesoscopic Flow Performance

- Subvolume size $h = 1 \, \mu\text{m}$, flow speed $v = 0.1 \, \text{mm/s}$

Mesoscopic Flow
Dependence on Subvolume Size

- Flow speed $v = 0.4 \text{ mm/s}$, distance $l_{RX} = 2 \mu\text{m}$

Mesoscopic Flow
Dependence on Subvolume Size

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Mesoscopic Flow
Dependence on Subvolume Size

- Flow speed $v = 0.4 \text{ mm/s}$, distance $l_{RX} = 2 \mu\text{m}$

• **Flow speed** $v = 0.4\, \text{mm/s}$, distance $l_{RX} = 2\, \mu\text{m}$

• Flow speed $v = 0.1 \text{ mm/s}$, distance $l_{RX} = 10 \mu\text{m}$

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Long Term Objectives

Question
How to design small systems with both living and synthetic devices where we can predict and control behaviour?

Biology

Communications and Signal Processing

Simulation of Reaction-Diffusion Systems A. Noel 39/46
Long Term Objectives

Question
How to design small systems with both living and synthetic devices where we can predict and control behaviour?

On-going topics
Use communications and signal processing tools to model:

- **Behavioural dynamics** of the system
- Devices’ ability to **share information** (including living “devices”)
Heterogeneous Quorum Sensing

Cell Type A

Cell Type B

Cell Type C

Noel, Fang, Yang, Makrakis, Eckford, https://arxiv.org/abs/1711.04870
Heterogeneous Quorum Sensing

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Tumour Growth and Development

Tissue Cells

Tumor Cells

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Heterogeneous Quorum Sensing

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The Idea

Noisy signalling contributes uncertainty for us to mitigate or enhance

Noel, Fang, Yang, Makrakis, Eckford, https://arxiv.org/abs/1711.04870
**Optogenetics** lets us externally stimulate neurons

- What are the limits to generate **any kind of spike train**?
- We are constrained by a neuron’s membrane potential dynamics

Biochemical reactions occur with significant randomness. Gillespie method initially intended for chemical reactions.

How much information can be transmitted in a reaction?

How well can we statistically characterize the evolution of a chemical reaction?
Background

The AcCoRD Simulator

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Conclusions
Communications engineering can be applied to reaction-diffusion modelling
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We want to predict and control behaviour in small natural environments
Conclusions

Communications engineering can be applied to reaction-diffusion modelling

We want to predict and control behaviour in small natural environments

Going Forward

Many open questions in behavioural dynamics and information transfer
Acknowledgements

- Primary collaborators on simulation work:
  - D. Makrakis (University of Ottawa)
  - J. Yang, Y. Wang (Australian National University)

- Funding
  - Natural Sciences and Engineering Research Council of Canada (NSERC)
The End
Thank you for your time and attention!

Homepage: www.warwick.ac.uk/adamnoel

AcCoRD Simulator:
www.warwick.ac.uk/adamnoel/software/accord/
Point vs Spherical Receiver

$\overline{N}_{RX}(t)$ – number of molecules expected at RX as a function of time

### 3D Point Receiver Observation (Point TX) – “Classical” Result

\[
\overline{N}_{RX}(t) = \frac{NV_{RX}}{(4\pi Dt)^{3/2}} \exp \left( -\frac{d^2}{4Dt} \right)
\]

### 3D Spherical Receiver Observation (Point TX)

\[
\overline{N}_{RX}(t) = \frac{N}{2} \left[ \text{erf} \left( \frac{r_{RX} - d}{2\sqrt{Dt}} \right) + \text{erf} \left( \frac{r_{RX} + d}{2\sqrt{Dt}} \right) \right] + \frac{N}{d} \sqrt{\frac{Dt}{\pi}} \left[ \exp \left( -\frac{(d + r_{RX})^2}{4Dt} \right) - \exp \left( -\frac{(d - r_{RX})^2}{4Dt} \right) \right]
\]

Point vs Volume Transmitter

1D Receiver Observation (Point TX)

\[ \overline{N}_{RX}(t) = \frac{N}{2} \left( \text{erf} \left( \frac{r_{RX} + d}{2\sqrt{Dt}} \right) - \text{erf} \left( \frac{d - r_{RX}}{2\sqrt{Dt}} \right) \right) \]

1D Receiver Observation (Volume TX)

\[ \overline{N}_{RX}(t) = \frac{N}{2r_{TX}} \left\{ \sqrt{\frac{Dt}{\pi}} \left[ \exp \left( -\frac{(x_{f} + r_{RX})^2}{4Dt} \right) - \exp \left( -\frac{(x_{f} - r_{RX})^2}{4Dt} \right) - \exp \left( -\frac{(x_{i} + r_{RX})^2}{4Dt} \right) \right. \\
+ \exp \left( -\frac{(x_{i} - r_{RX})^2}{4Dt} \right) \right] + \frac{1}{2} \left[ (x_{f} + r_{RX}) \text{erf} \left( \frac{x_{f} + r_{RX}}{2\sqrt{Dt}} \right) \\
- (x_{i} + r_{RX}) \text{erf} \left( \frac{x_{i} + r_{RX}}{2\sqrt{Dt}} \right) - (x_{f} - r_{RX}) \text{erf} \left( \frac{x_{f} - r_{RX}}{2\sqrt{Dt}} \right) + (x_{i} - r_{RX}) \text{erf} \left( \frac{x_{i} - r_{RX}}{2\sqrt{Dt}} \right) \right] \} \]