Using Molecular Communication to Understand and Improve Chemical Signaling

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What?

Molecular Communication

- How do biological systems **share information?**
- What are the practical **communication limits?**
- **Molecules** are commonly used between cells, tissues, organisms

Image: US CDC `http://www.cdc.gov/tb/education/corecurr/pdf/chapter2.pdf`

Why Study Molecular Communication?

Why are we (from communications and signal processing) interested in *Molecular Communication* for signaling?

- We can **help understand biological systems**
- We can **help interface with biological systems**
- We can **gain inspiration for design** of synthetic networks

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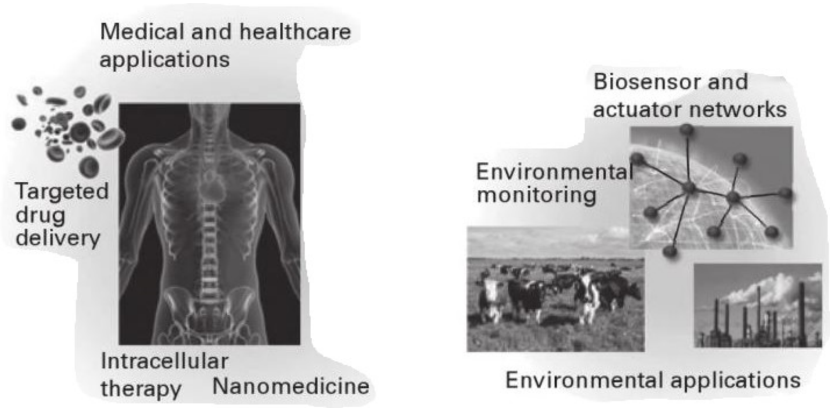
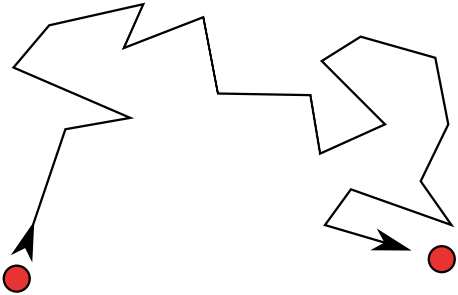
Biological Signaling $\Longleftrightarrow$ Communications and Signal Processing



Edited Image From: Nakano, Eckford, Haraguchi, *Molecular Communication*. Cambridge University Press, 2013.

How are Molecules Transported?

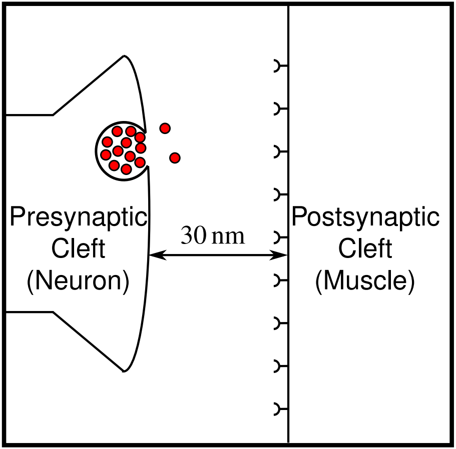


Diffusion – transport by colliding with other molecules

- **No external energy** or infrastructure required
- **Very fast** over "short" distances ($\leq 1\mu$m)
- Used by **many processes in cells**

Examples in Biology

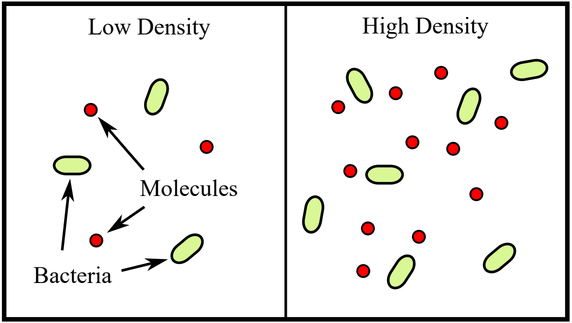
1) Neuromuscular Junction



- Motor neuron to muscle fiber
- Molecules released ($\sim 10^4$)
- Reception $\rightarrow$ contraction
- Up to 50 **times per second**

Examples in Biology

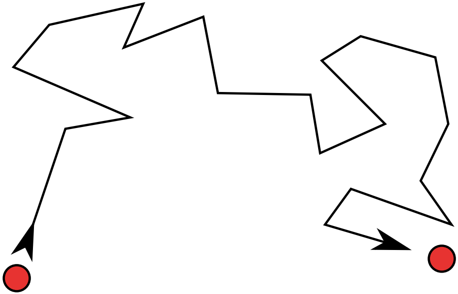
2) Quorum Sensing in Bacteria



- Bacteria release molecules
- Individual bacteria estimate population density
- Bacteria **favor cooperative behavior** when density is high

Unique Features of MC Systems

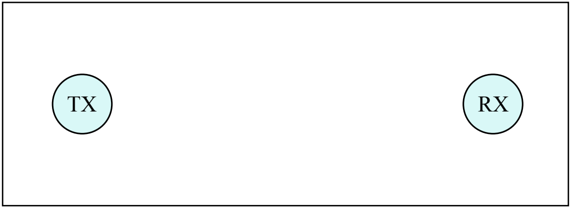
What Distinguishes MC from Conventional Communications Analysis?



Features of diffusive molecular communication systems:

- **Discrete objects** – physically collected and transported
- **Uncertainty in diffusion trajectory** of each molecule
- Environmental phenomena – e.g., **chemical reactions, fluid flow**
- **Limited computational resources** – small devices such as cells

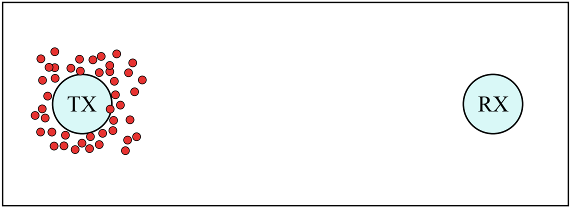
The Diffusive Channel



Consider a single transmitter (TX) and receiver (RX)

- Molecules are **released by TX**
- RX makes observations
- Describe channel with the **channel impulse response (CIR)**
- CIR may not be tractable – Need **simplifying assumptions**

The Diffusive Channel



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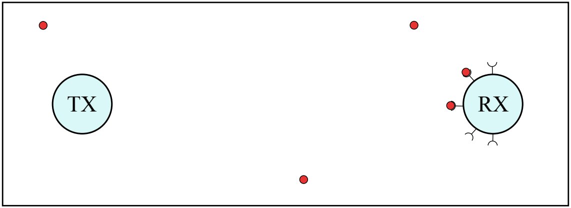

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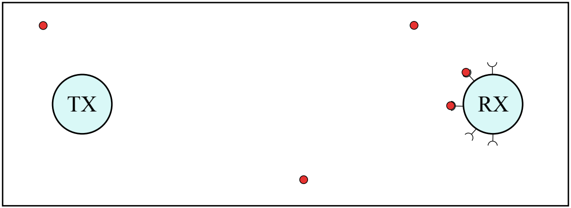
Point vs Volume Devices

Point-to-Point Assumption

Common to model TX and RX as points. Is this assumption accurate?



Other assumptions:

- Instantaneous release of N molecules by TX
- Molecules diffuse with diffusion coefficient D
- Distance between TX and RX is fixed at d
- RX has a **passive surface** that molecules can diffuse through

Point vs Spherical Receiver

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

3D Point Receiver Observation (Point TX) – "Classical" Result

$$\overline{N}_{\mathrm{RX}}(t) = \frac{N V_{\mathrm{RX}}}{(4\pi D t)^{3/2}} \exp\left(-\frac{d^2}{4Dt}\right)$$

3D Spherical Receiver Observation (Point TX)

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

Noel, Cheung, Schober, *Proc. IEEE ICC MoNaCom*, Jun. 2013.

Point vs Volume Transmitter

Don't worry, this is the last slide focusing on math ...

1D Receiver Observation (Point TX)

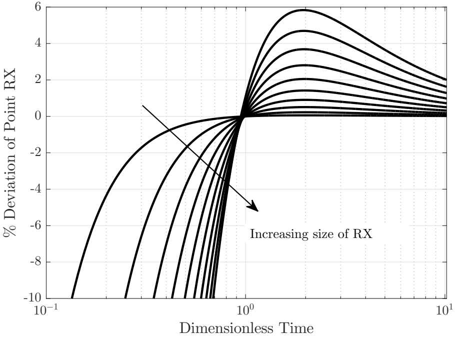
$$\overline{N}_{\mathsf{RX}}\left(t\right) = \frac{N}{2}\left(\mathrm{erf}\left(\frac{r_{\mathsf{RX}}+d}{2\sqrt{Dt}}\right) - \mathrm{erf}\left(\frac{d-r_{\mathsf{RX}}}{2\sqrt{Dt}}\right)\right)$$

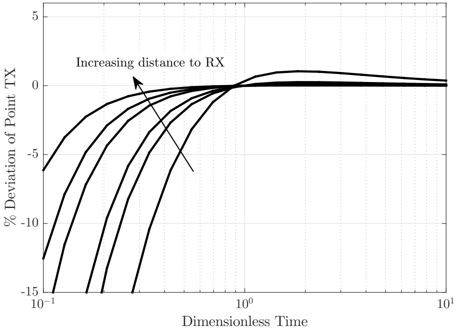
1D Receiver Observation (Volume TX)

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

Noel, Makrakis, Hafid, *Proc. CSIT BSC*, Jun. 2016.

Point-to-Point Assumption





Accuracy of Point-to-Point Assumption

Accuracy improves as relative distance between TX and RX increases

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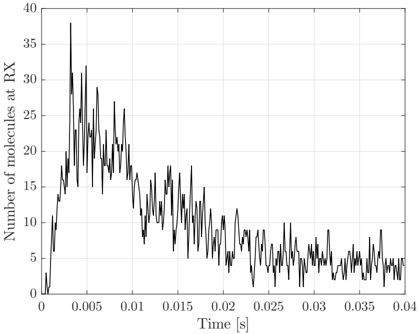
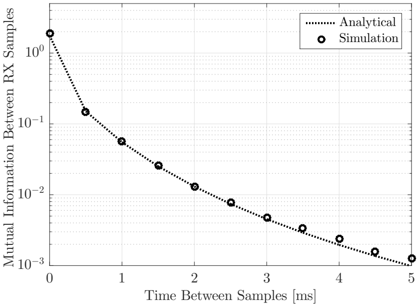
Noel, Cheung, Schober, *Proc. IEEE ICC MoNaCom*, Jun. 2013.

Noel, Makrakis, Hafid, *Proc. CSIT BSC*, Jun. 2016.

Independence of Molecule Counting

Molecules enter and leave RX – usually assume independent samples





Accuracy of Observation Independence

Accuracy improves as time between consecutive samples increases

Noel, Cheung, Schober, *IEEE Trans. NanoBiosci.*, Sept. 2014.

Reactive Surfaces

Passive RX – No affect on molecule propagation

- Easier to simulate
- Easier to analyze (exponentials)
- Some biological justification

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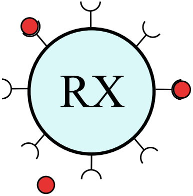
Active RX – Model chemical detection of molecules

- More realistic
- Harder to simulate
- Less convenient analysis (error functions)

Reactive Surfaces



Summary of our results with reactive surfaces:

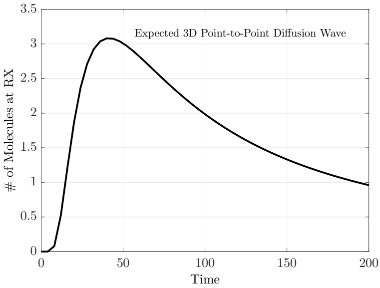
- Derived **CIR for reversible adsorption**, where molecules can stick and detach from RX surface
- Measured impact of **multiple absorbing RXs**
- Derived transforms to **convert between signals at passive and absorbing RXs**

Deng, **Noel**, Elkashlan, Nallanathan, Cheung, *IEEE Trans. Mol. Biol. Multi-Scale Commun.*, Dec. 2015.

Lu, Higgins, **Noel**, Leeson, Chen, *IEEE Trans. NanoBiosci.*, to appear.

Noel, Deng, Makrakis, Hafid, *Proc. IEEE Globecom*, Dec. 2016.

Modifying the Communications Channel



Challenges with diffusion:

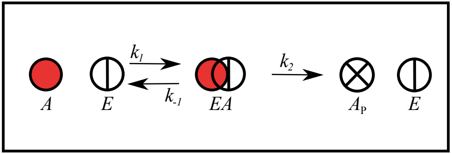
- **Propagation time increases** with square of distance
- Significant **intersymbol interference (ISI)**

Natural diffusive channels have modifications that improve signaling

- Neuromuscular junction has **molecule degradation**
- Blood vessels have **bulk fluid flow**

Molecule Degradation to Reduce Interference

Neuromuscular junction has enzymes



Noel, Cheung, Schober, *IEEE Trans. NanoBiosci.*, Mar. 2014.

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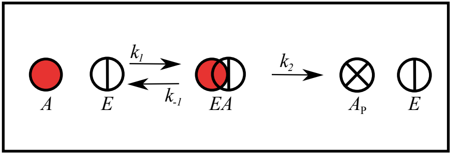
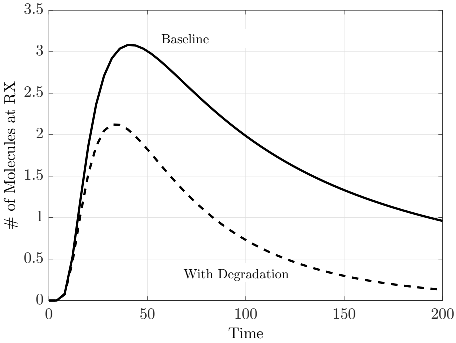


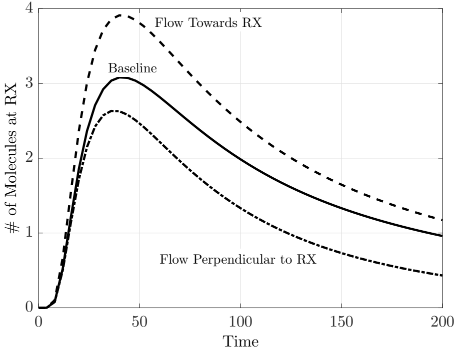


Impulse Response with Degradation

$$\overline{N}_{\text{RX}}(t) \approx \frac{NV_{\text{RX}}}{(4\pi Dt)^{3/2}} \exp\left(-kt - \frac{d^2}{4Dt}\right)$$

Noel, Cheung, Schober, *IEEE Trans. NanoBiosci.*, Mar. 2014.

Net Fluid Flow



Impulse Response with Flow

$$\overline{N}_{\text{RX}}(t) = \frac{NV_{\text{RX}}}{(4\pi Dt)^{3/2}} \exp\left(-\frac{(d - v_{\parallel} t)^2 + (v_{\perp} t)^2}{4Dt}\right)$$

Noel, Cheung, Schober, *IEEE Trans. NanoBiosci.*, Sept. 2014.

Channel Parameter Estimation Problem

Can we estimate the underlying channel parameters (distance, diffusion coefficient, etc.)? Why would we do this?

- Local **monitoring and diagnostics** applications
- **Tuning** transceiver parameters

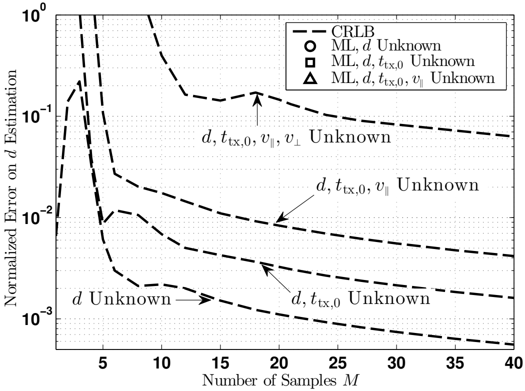
Consider RX taking M samples of an impulse response:

- Derived **Cramer Rao lower bound (CRLB)**
- Compared CRLB with **Maximum Likelihood** estimator
- Assessed **simpler estimators** using peak of impulse response

Channel Parameter Estimation Problem

Results

Consider estimating the distance:



- CRLB increases as fewer parameters known
- ML is asymptotically efficient

Noel, Cheung, Schober, *IEEE Trans. Mol. Biol. Multi-Scale Commun.*, Mar. 2015.

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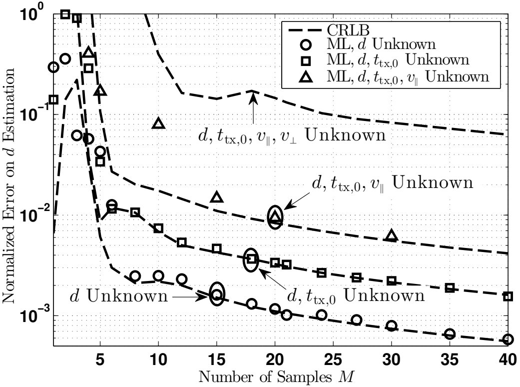

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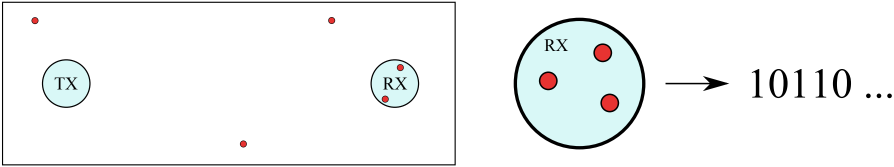
The Communication Problem

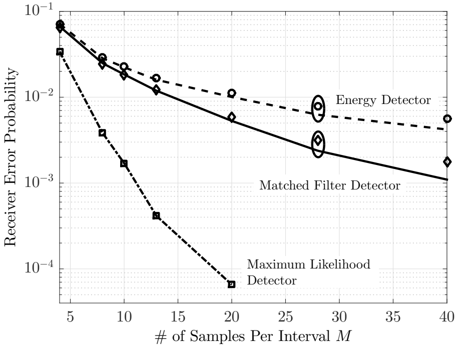


How to design a communication system?

- Different ways to modulate (time of release, # of molecules, etc.)
- Focus on impulsive **binary ON/OFF keying**
- Detect using **multiple RX samples per symbol** interval

Optimal vs Suboptimal Detection

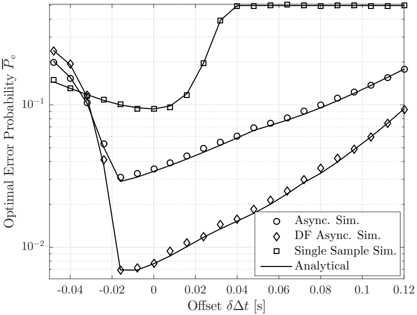
- **Energy detector** and **matched filter** with constant decision thresholds
- **Maximum Likelihood** detector based on Viterbi algorithm
- We can approach ML performance with molecule degradation and/or strong flow (not shown)



Noel, Cheung, Schober, *IEEE Trans. NanoBiosci.*, Sep. 2014.

Asynchronous Communication

Consider RX with **imperfect timing information**:

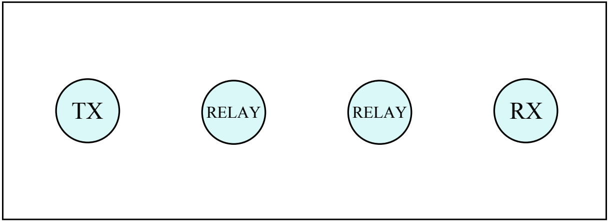


- Single sample detector uses *expected* peak
- **Asynchronous detector uses peak** in sampling interval
- Asynchronous detector **more resilient to timing offsets**
- Additional improvement with **decision feedback (DF)**

Noel and Eckford, *IEEE ICC 2017*, submitted.

Multi-Hop Relaying

Can we use relays to reach **further destinations faster**?



Consider decode-and-forward and amplify-and-forward relaying

- Various schemes for **re-using molecule types** in different hops
- Identified **self-interference (SI)** and **backward ISI (BI)**
- Applied **decision feedback** to adjust RX and relay thresholds

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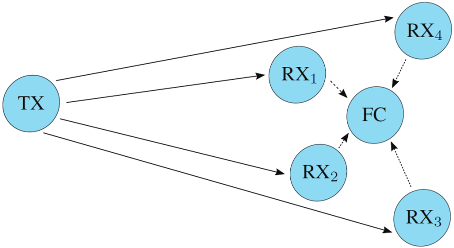
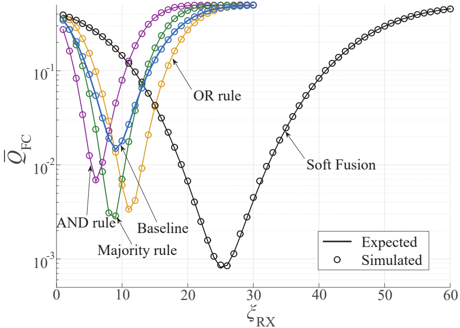
Ahmadzadeh, **Noel**, Schober, *IEEE Trans. Mol. Biol. Multi-Scale Commun.*, Jun. 2015.

Ahmadzadeh, **Noel**, Burkovski, Schober, *Proc. IEEE GLOBECOM*, Dec. 2015.

Cooperative Detection

There is limited work about MC devices actually "cooperating"





Consider multiple RXs communicating with a **fusion center (FC)**

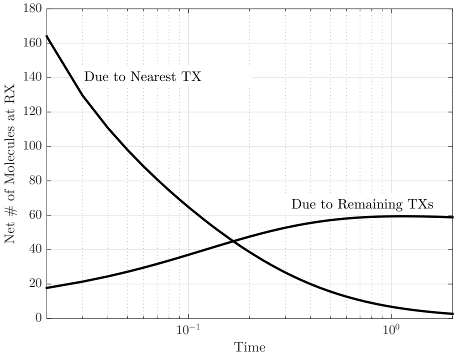
- **Derived FC performance** when RXs make hard decisions
- Optimize RX and FC decision thresholds as a **convex problem**

Fang, **Noel**, Yang, Eckford, Kennedy, *IEEE Trans. Mol. Biol. Multi-Scale Commun.*, submitted.

Very Large Networks

What if we have a **very large number of TXs**?

- Can we communicate with **closest TX**?
- Derived channel response of closest vs remaining TXs
- Considered RX design when **all TXs transmitting together**
- Significant interference from distant TXs



Deng, **Noel**, Guo, Nallanathan, Elkashlan, *IEEE Trans. Mol. Biol. Multi-Scale Commun.*, submitted.

Existing Simulator Options

There are 2 broad categories of simulator available:

1. Reaction-diffusion solvers
   - From the physical-chemistry community
   - Generic **"sandbox" tools to customize environments**
   - Not designed for communications (e.g., transceivers, statistics)
2. Molecular communication simulators
   - From the communications engineering community
   - **Designed for communications research**
   - Constrained environmental design options

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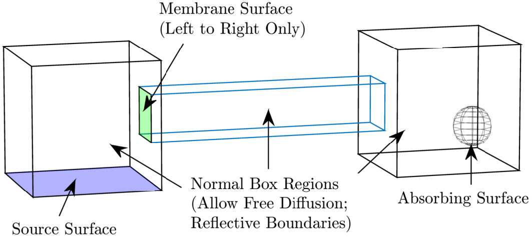
- Need: A “sandbox” simulator for communications research in reaction-diffusion systems
  - Improve learning curve for multi-disciplinary field
  - Encourage use of simulations

AcCoRD Simulator

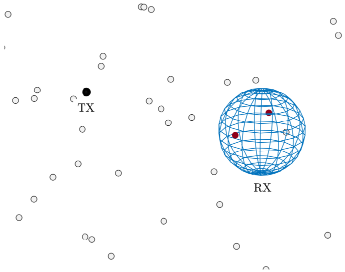


AcCoRD (**Ac**tor-based **Co**mmunication via **R**eaction-**D**iffusion)

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

Noel, Cheung, Schober, Makrakis, Hafid, *Nano Commun. Networks*, submitted.

AcCoRD Accessibility



Usability features:

- **Open source** development on Github
- Online user documentation
- Many **sample configurations** available
- Post-processing in **MATLAB** (figures, videos)

Noel, Cheung, Schober, Makrakis, Hafid, *Nano Commun. Networks*, submitted.

Long Term Objectives

What is the Big Picture?

Why are we (from communications and signal processing) interested in *Molecular Communication* for signaling?

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Overall Direction

Use communications and signal processing tools to:

- **Improve the understanding** of biochemical processes
- **Interact/manipulate** at a microscopic level

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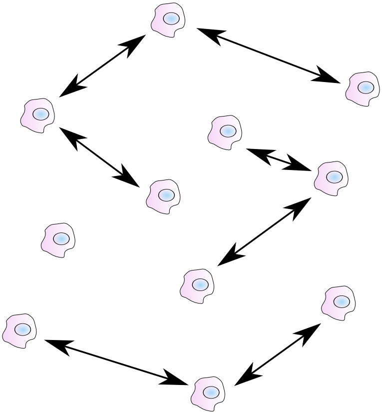
Ultimate Goal

Advance **medical treatments and other applications** that rely on detecting molecular signals

Non-Ideal Transceivers

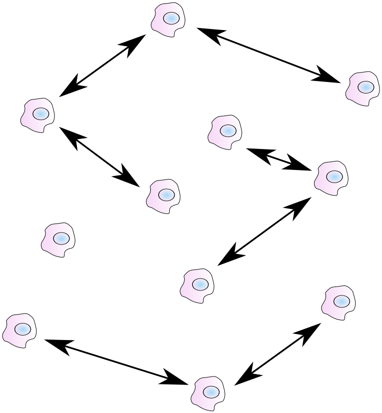
We assume devices **always behave as intended**



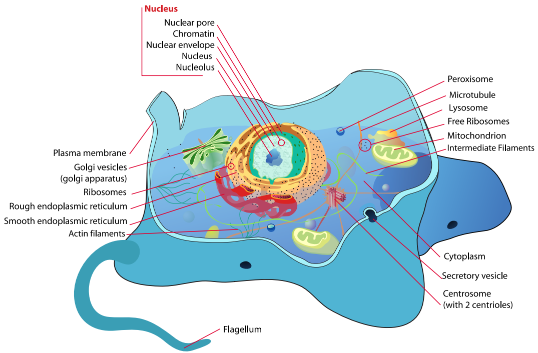
- Devices may unintentionally **disrupt or interfere** with natural system
- Devices **may not cooperate** as desired
- Can we gain insight into how we can **predict and control** node behavior?

Group Dynamics

- What if devices behave **selfishly**?
- Could a device **benefit by disrupting** common signals? (e.g., consuming molecules)
- What **incentives** exist for cooperation?
- **Game theory** could be applied to study these dynamics



Toxicity and Interference

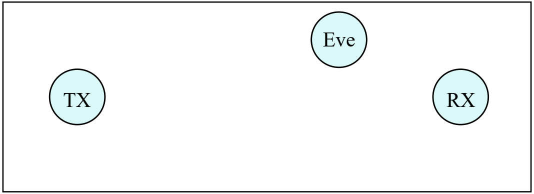


- Cellular complexity is devoted to **maintaining a healthy state**
- Many molecules have **target concentration ranges**
- How can we **avoid toxicity** when introducing new signaling?
- **How much information** can we transmit and respect constraints?

Image: Wikimedia Commons `https://commons.wikimedia.org/wiki/File:Animal_cell_structure_en.svg`

Link Security

Does the conventional eavesdropper problem make sense here?



Some potential security-related problems:

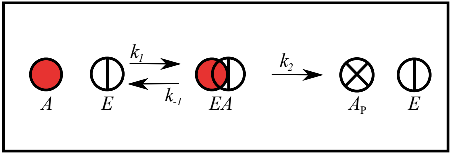
- Can we **detect a “malicious node”** (e.g., tumor)?
- Can we **disrupt a diseased cell** that uses signaling to spread?
- Can we **avoid detection** by immune system?

Measuring Neural Impulses

- Nerve cells (neurons) **propagate impulsive signals**
- Experiments have **externally triggered** neural impulses
- Both **number and timing** of action potentials are important
- How reliably can we **generate a target impulse train?**

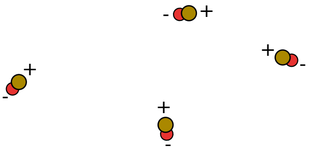
Image: Wikimedia Commons https://commons.wikimedia.org/wiki/File:Neural_signaling.PNG

Mutual Information of Chemical Reactions



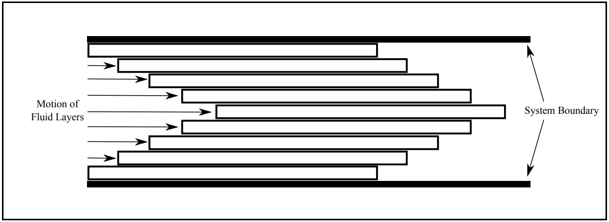
- Biochemical reactions occur with **significant stochasticity**
- **How much information can be transmitted** in a reaction?
- Can we **measure the mutual information** between samples of reaction output?

Improving Channel Models



Other physical phenomena can also modify molecule trajectories:

- Diffusion of **polar or charged molecules**
- Impact of **electric fields** (internal and/or external)
- Non-uniform flow (e.g., **laminar flow** in small blood vessels)



Final Words

- Molecular communication **combines communications and biological signaling**
- MC offers **new perspectives** on communications analysis
- **Interact with biochemical processes** at a microscopic level
- Inspiration between biology and engineering is **bidirectional**

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That's All, Folks

Thanks for your time and attention!

Papers and AcCoRD Simulator: `www.adamnoel.ca`