Optimizing Rate of Hormone Clearance to Maximize Channel Capacity in the Bloodstream

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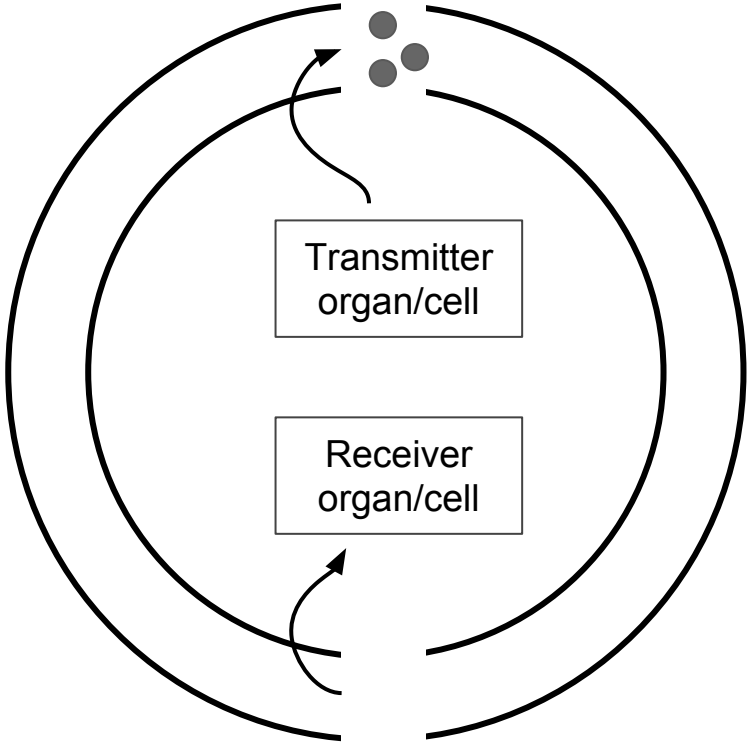
MAS.862 Final Project

Hormones act as messengers in the circulatory system

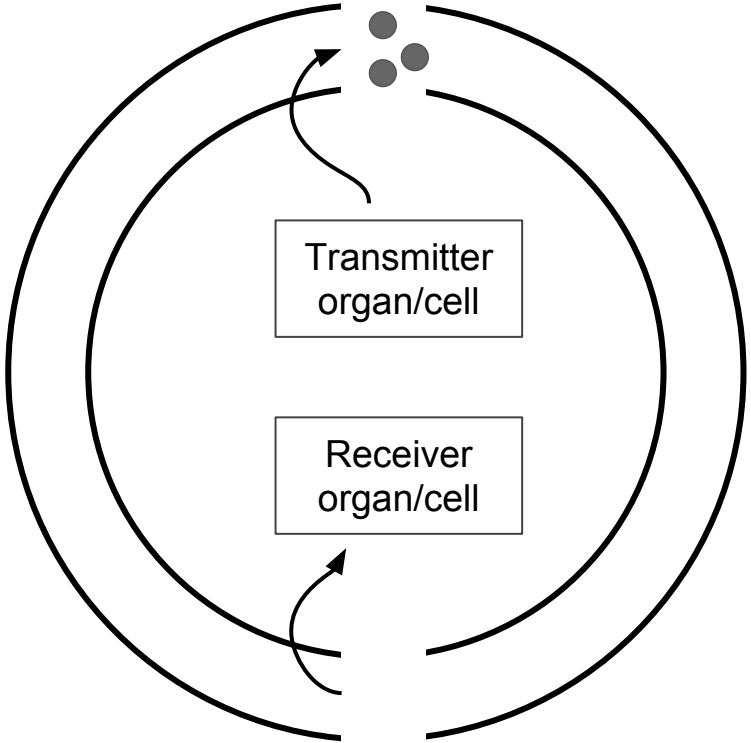


In molecular communication,

Hormones are secreted at some rate, *F*, at TX.

The presence of molecule above a threshold, *T*, at RX = 1
The absence of a molecules (or below threshold *T*) at RX = 0

Hormones are transported by diffusion, advection, and absorption



Diffusion

Advection

Clearance

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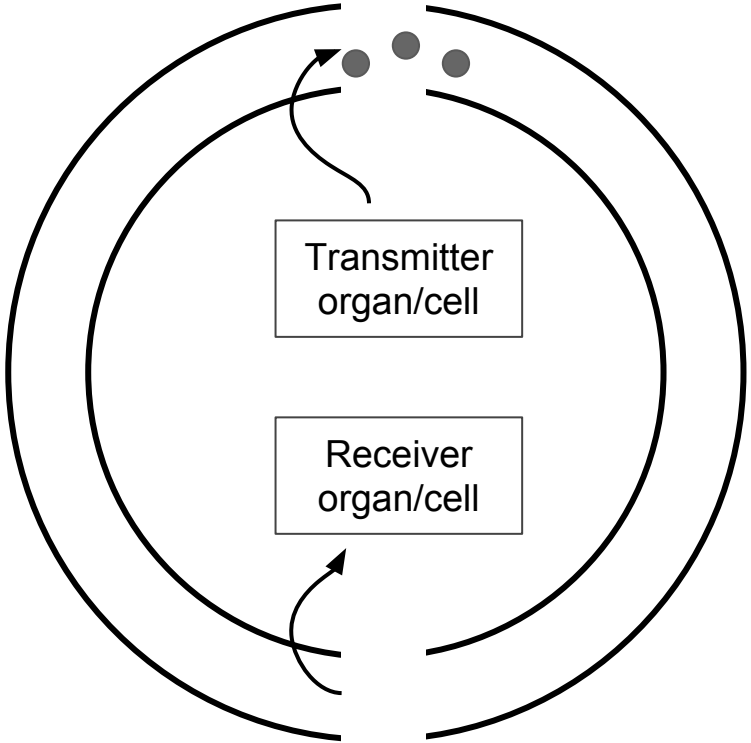


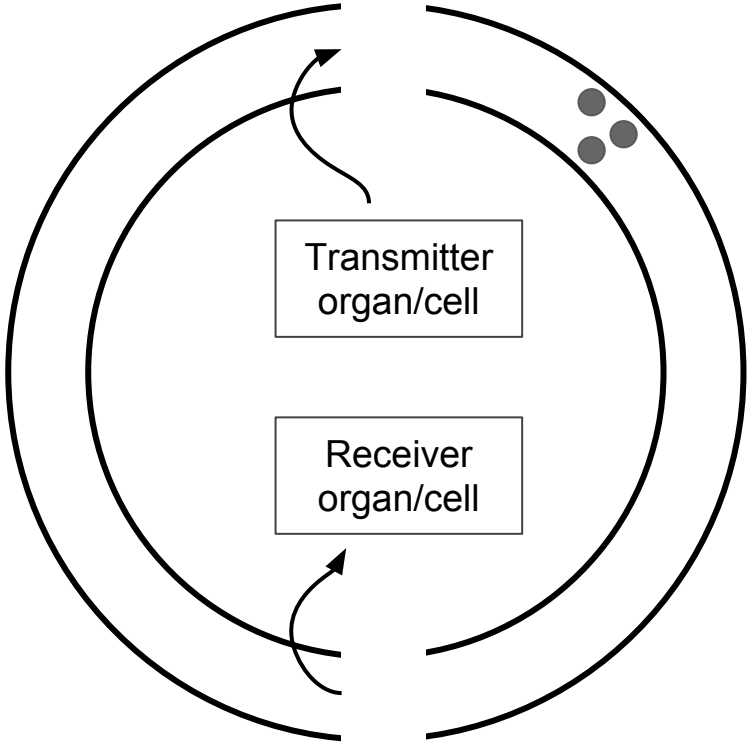
Diffusion

$$\frac{\mathrm{d}C}{\mathrm{d}t} = D\frac{\mathrm{d}^2C}{\mathrm{d}x^2}$$

Advection

Clearance

Hormones are transported by diffusion, advection, and absorption



Diffusion

$$\frac{\mathrm{d}C}{\mathrm{d}t} = D\frac{\mathrm{d}^2C}{\mathrm{d}x^2}$$

Advection

$$\frac{\mathrm{d}C}{\mathrm{d}t} = -v\frac{\mathrm{d}C}{\mathrm{d}x}$$

Clearance

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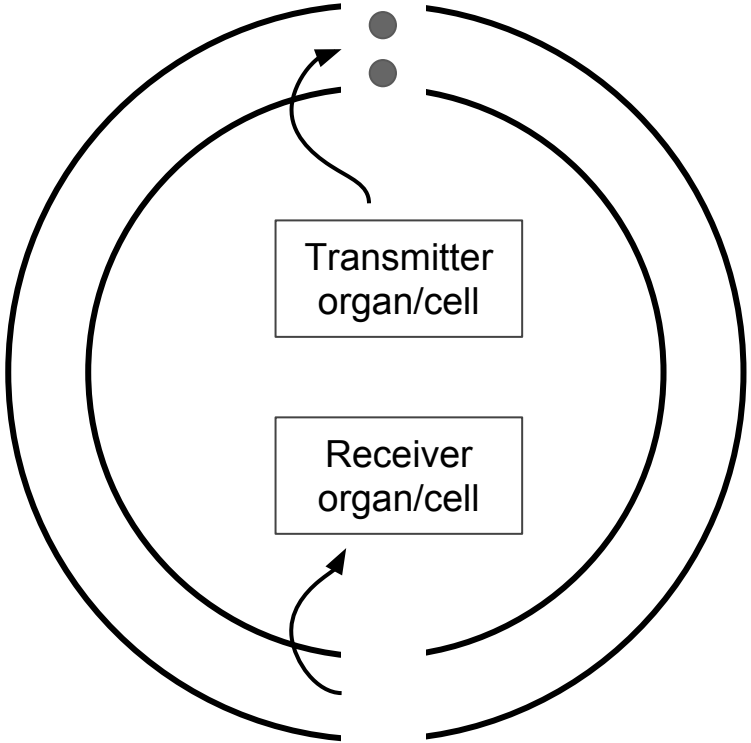


Diffusion

$$\frac{\mathrm{d}C}{\mathrm{d}t} = D\frac{\mathrm{d}^2C}{\mathrm{d}x^2}$$

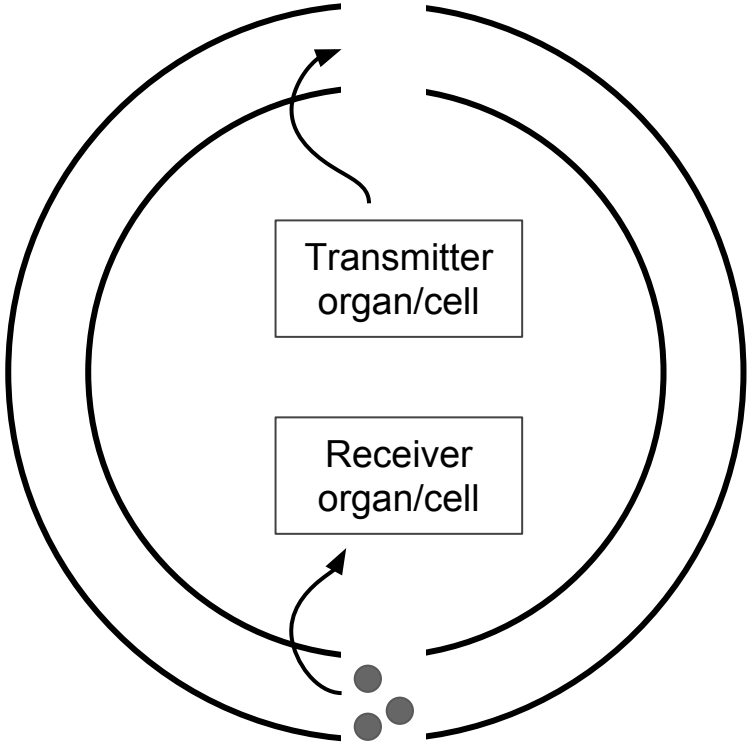
Advection

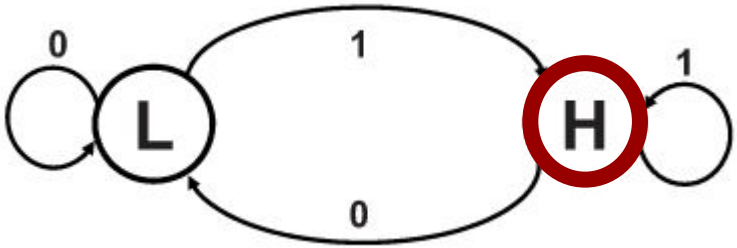
$$\frac{\mathrm{d}C}{\mathrm{d}t} = -v\frac{\mathrm{d}C}{\mathrm{d}x}$$

Clearance (absorption)

$$\frac{\mathrm{d}C}{\mathrm{d}t} = -RC$$

Channel capacity is determined by amount of time needed to switch states





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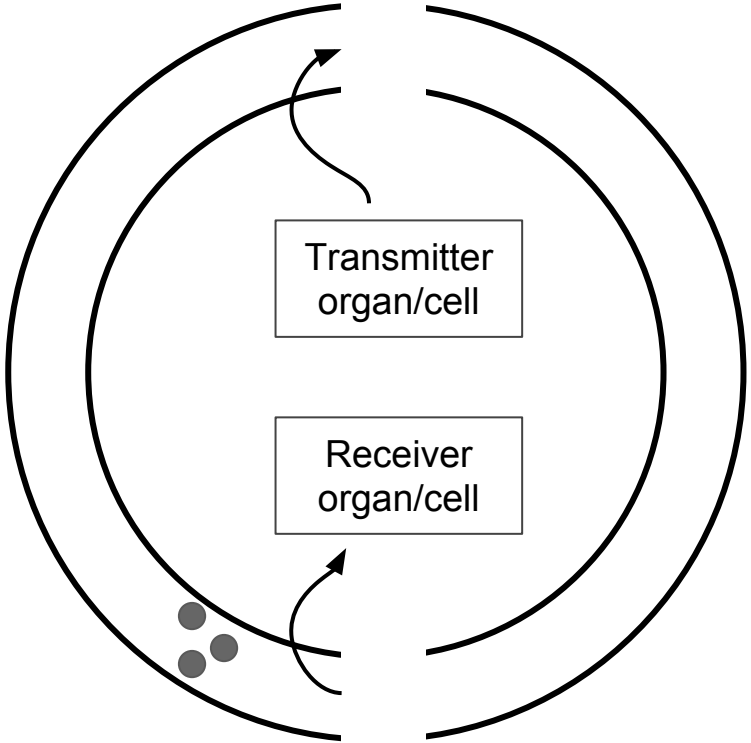

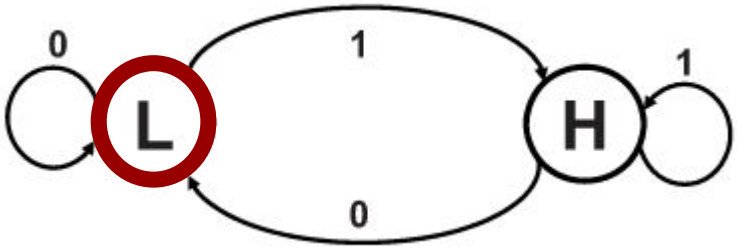

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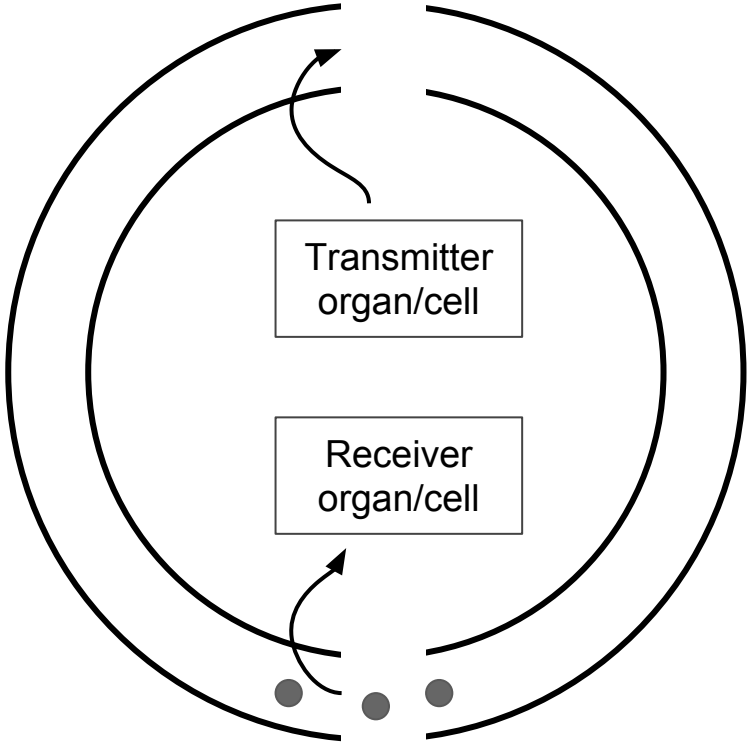
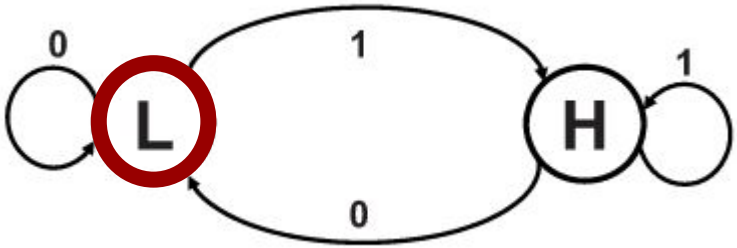
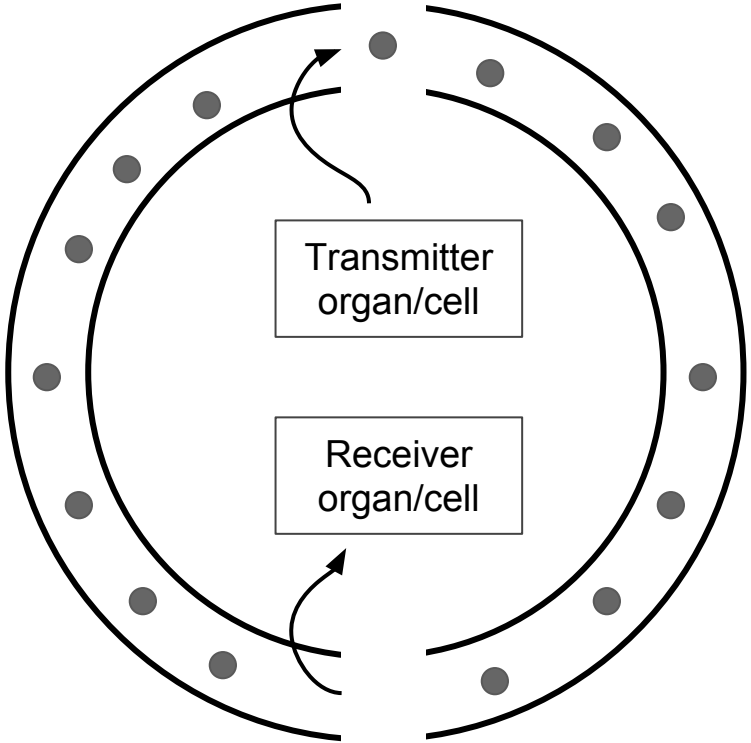




Noisy molecule positions make the transition hard to distinguish

Because it is a closed system, “noise floor” is a result of remnant molecules



Since it eliminates remnant molecules, *clearance* may play an important factor in setting the channel capacity!

Prior Work

1. What is the channel capacity of a diffusion-based molecular system? No unified theory, but:

- State-space approach to model information in molecular comm. (Fekri) [1]
- Memory and noise from a thermodynamic perspective (Akyildiz) [2]
- Approximating noise as Gaussian to use classic Shannon (Goldsmith) [3]

2. How to estimate channel capacity of the bloodstream?

- Models probability distribution of CO_2 in different physiological conditions to come up with entropy and information limits (Yamamoto)

No discussion of clearance-limited noise floor in prior literature. **Is the clearance relevant to channel capacity? Is the clearance optimized to maximize channel capacity in biological system?**

Problem 1: Cellular Transport

If the bloodstream is treated as 1D, and a transmitter cell releases a unit impulse of molecules, what will the distribution of molecules look like when it arrives at a receiver cell a distance L down the bloodstream? Assume that clearance occurs at a very different time scale than diffusion.

How does the peak concentration change (approximately) if instead of an impulse initial condition, there is instead a short rectangular pulse of time τ, with a rate (amplitude) F? Specify any assumptions you use.

Solution 1: Cellular Transport

First, let us assume that a single velocity, v describes the advection of molecules in the system. This doesn't mean that the velocity is constant, but rather all of the molecules experience an average velocity $v \equiv \frac{1}{L}\int_0^L v(x)dx$ by the time they reach a position $x \approx L$. In this case, advection acts simply to change the frame of reference from $C(x,t)$ to $C(x-vT, t+T)$ after a time T independent of other processes in the system.

T = L/v

The diffusion of molecules will produce the well-known impulse response of

$$h(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}} [1 \cdot \text{mol}]$$

. The impulse response to clearance is

$$h(x,t) = \delta(x) e^{-Rt}$$

If the two processes occur at very different time scales, then the impulses responses can be multiplied together in time to get

$$h(x,t) = \frac{e^{-Rt}}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}} [1 \cdot \text{mol}]$$

Solution 1: Cellular Transport

Bringing back advection, we simply change frames to get

$$h(x = L, t = T) = \frac{e^{-RT}}{\sqrt{4\pi DT}} e^{-\frac{(x-L)^2}{4DT}} [1 \cdot \text{mol}]$$

The peak concentration here is clearly at $x = L$ and is given by $\frac{e^{-RT}}{\sqrt{4\pi DT}}$.

Now, if we want to know the response to a rectangular pulse, we convolve $h(x, t)$ with the rectangular pulse. The rectangular pulse has a width τv in space. If this width is much smaller than the standard deviation of the Gaussian impulse response above, then we are essentially convolving two rectangular functions. So, if $\tau v \ll \sqrt{4DT}$, then the peak concentration at $x = L$ becomes

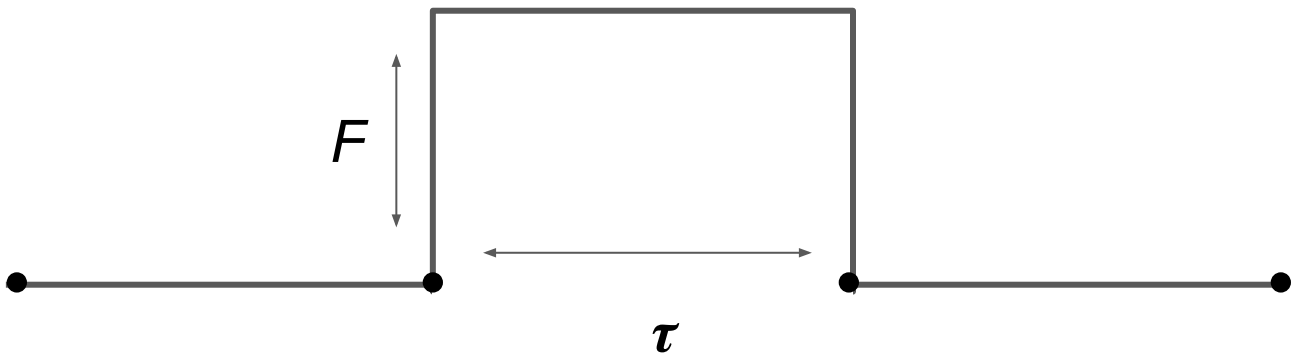
$L \gg v\bar{\tau}$

$$C(x = L, t = T) = \frac{F\tau e^{-RT}}{\sqrt{4\pi DT}}$$

(We note in passing that the peak concentration at L may occur slightly before T, but we neglect that difference here)

Problem 2: Equilibrium "Noise Floor"

The release of molecules is determined by cellular processes and biochemical feedback for the hormone of interest. Let us assume that the transmission happens at a frequency *f* (this could range from every few seconds to hours) in a pulsatile waveform of duration τ and amplitude *F*, what is the equilibrium concentration of molecules in the bloodstream, C_0?



Solution 2: Equilibrium "Noise Floor"

Neither diffusion nor advection change the total number of molecules, so at equilibrium, we know that

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{fF\tau}{2L} - RC = 0$$

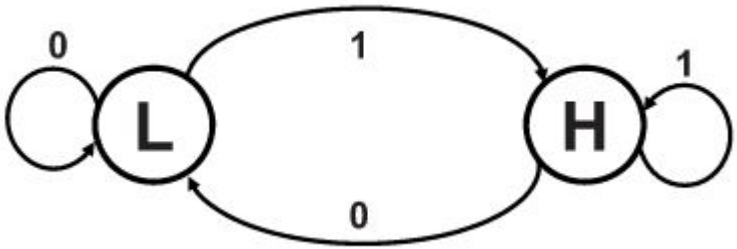
Note that we have somewhat arbitrarily chosen the entire length of the circulatory system as $2L$. This is because in quite a few applications, the transmitting organ is on the opposite end of the circulatory system. For example, the brain releases antidiuretic hormone (ADH), which is a signal to the kidneys.

Let $C_0 \equiv$ the equilibrium concentration. We solve to get

$$C_0 = \frac{fF\tau}{2LR}$$

Problem 3: Pulse Time Needed for State Transitions

If the equilibrium concentration of the molecules in the bloodstream is C_0, a reasonably sensitive receiver cell may decide to change states to “H” if it detects a hormone level of $>2C_0$ and may transition back to “L” if it detects a hormone level of $\sim C_0$. If the cell can release hormones with a pulse amplitude F, what is the pulse release time τ required for a transition in both cases: L→ H and H → L?



Solution 3: Pulse Time Needed for State Transitions

To go from a concentration of C_0 to $2C_0$, the cell must release enough hormone such that the concentration of the hormone at $x = L$ increases by C_0. Thus, from part (1), we can write that

$$C_0 = \frac{F\tau_1 e^{-RT}}{\sqrt{4\pi DT}}$$

Solving for τ_1, I get

$$\tau_1 = \frac{C_0\sqrt{4\pi DT}}{Fe^{-RT}}$$

To drop from a concentration of C_0, the cell must simply not release any hormone. In this case, the concentration drops entirely due to clearance. The time it takes, τ_0, is given by:

$$2C_0 = C_0 e^{-R\tau_0}$$

$$\tau_0 = \frac{-\ln\frac{1}{2}}{R} \approx \frac{0.69}{R}$$

Problem 4: Channel Capacity

Assuming that (almost) all of the information is conveyed in the state transitions L → H and H → L which occur with equal probability, calculate the Shannon channel capacity for this channel.

Solution 4: Channel Capacity

If each transition has an equal chance of occurring, then the information carried with each signal is

$$-\log p_i = -\log 1/2 = 1 \text{ bit}$$

Let T be a long time. The information carried by this channel in a time T is given by $\frac{(2)T}{\tau_0+\tau_1}$. Thus the average channel capacity can be written as:

$$c = \frac{2}{\tau_0 + \tau_1}$$

Problem 5: Optimizing the Clearance Rate

Plot the channel capacity as a function of R. For what value of *R* is the channel capacity maximized with the parameters below for for the antidiuretic hormone (ADH) [4]? How close is this to the value of *R* obtained from literature (see table)? Verify all of the assumptions made above hold for ADH.

mol → pg, cm → mL

Physiological Parameters for ADH in the Human Body	
F [pg/sec]	2.5 [4]
C_o [pg/cm*]	0.033 [5,8]
D [cm^2/sec]	4.51×10^{-6} [6]
T [sec]	30 [7]
R [1/sec**]	0.012 [5,9,10]

* after multiplication by an average blood vessel area (1 mm^2) to go from pg/mL to pg/cm **Converted from pg/sec to 1/sec by total volume of glomerulus

Solution 5: Optimizing the Clearance Rate

Substituting our expressions from part (4), the channel capacity is equal to:

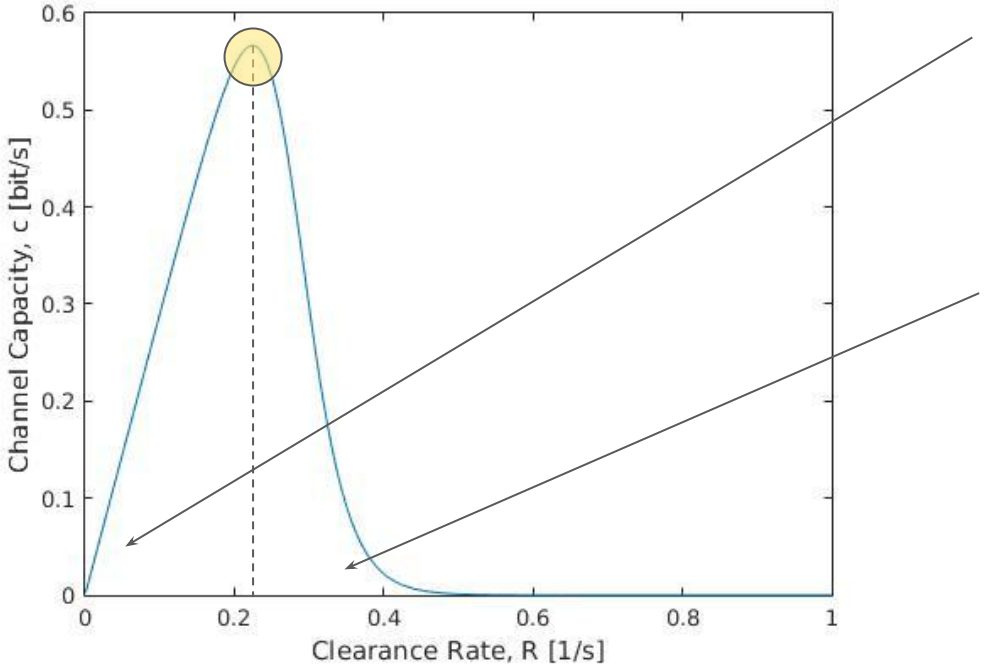
$$c = \frac{2}{\frac{C_0\sqrt{4\pi DT}}{Fe^{-RT}} + \frac{\ln 1/2}{R}}$$

Substituting values from literature,

$$c = \frac{2}{\frac{1}{1839e^{-R\cdot 30\,\mathrm{s}}} + \frac{0.69}{R}}$$

This takes a maximum for $R = 0.224\ \mathrm{s}^{-1}$ when $c = 0.57$ bits/s

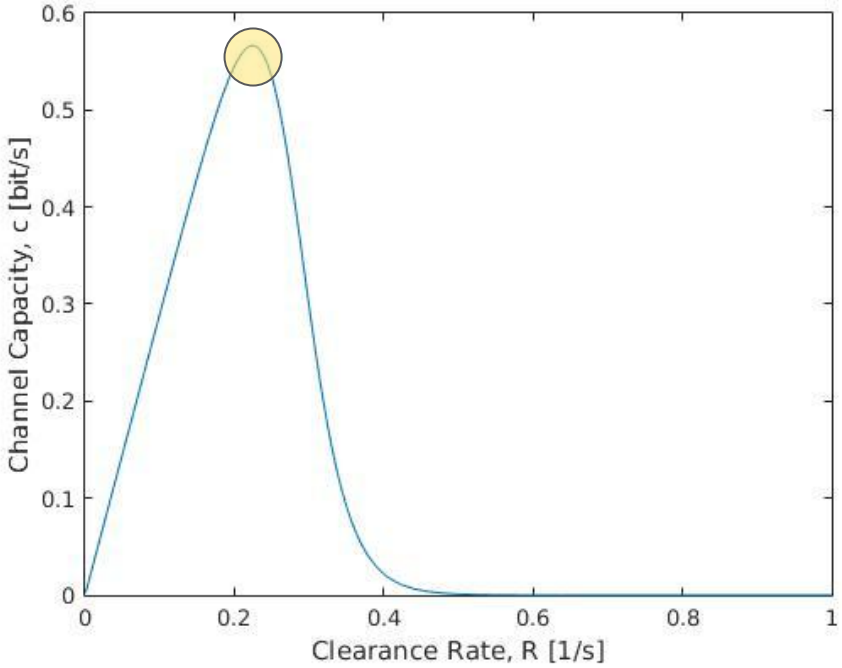
Solution 5: Optimizing the Clearance Rate

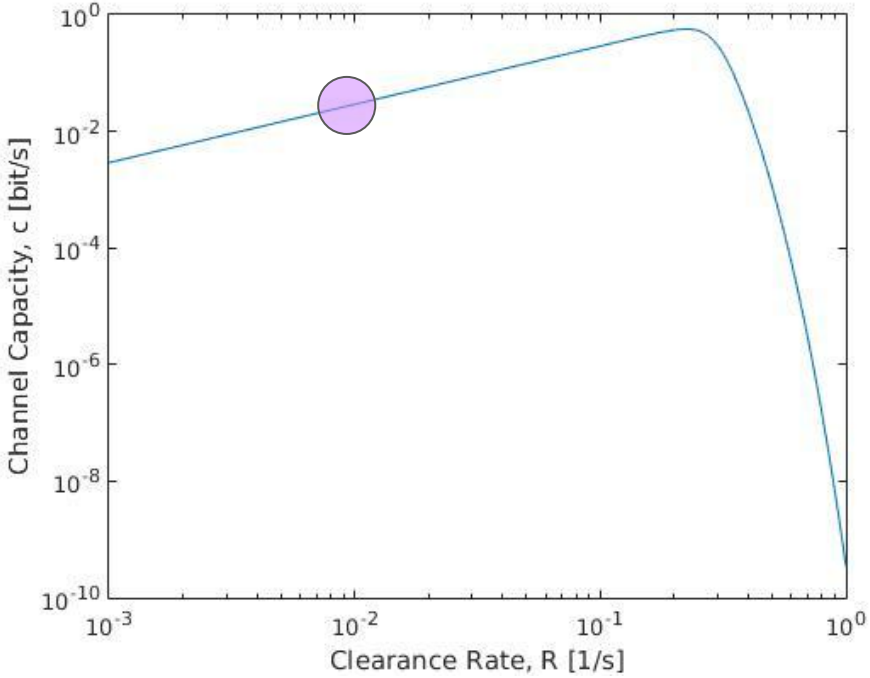


Slow clearance rate inhibits
H → **L** transition

Fast clearance rate inhibits
L → **H** transition

Solution 5: Optimizing the Clearance Rate





Implications and Future Plans

- We have developed an analytical expression for the channel capacity of the bloodstream that is extendable to a variety of hormones and molecules based on available information. We show that clearance does significantly affect channel capacity

- The clearance rate of ADH does not seem to be set to maximize channel capacity. However, for molecules that are part of faster biochemical feedback loops (like adrenaline, CO_2), the channel capacity may be closer to optimal. This should be verified for other molecules.

- We should also verify the many cellular biology assumptions (concentration threshold for signal transduction, etc.)

Questions?

???

References

1. http://www.mit.edu/~beirami/papers/ISIT11-capacity.pdf
2. http://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=6305481
3. http://arxiv.org/pdf/1602.07757v1.pdf
4. http://ac.els-cdn.com/0304394086903083/1-s2.0-0304394086903083-main.pdf?_tid=eff0269c-1b18-11e6-9c48-00000aacb35d&acdnat=1463370640_271d92232e0c122c67b8c1c8dc7643f6
5. http://www.ncbi.nlm.nih.gov/m/pubmed/6467834/
6. http://onlinelibrary.wiley.com/doi/10.1021/js960503w/epdf
7. http://www.lbc.co.uk/how-long-does-it-take-for-blood-to-flow-round-the-body-47277
8. http://www.encyclopedia.com/topic/Blood_vessels.aspx
9. http://www.ias-iss.org/ojs/IAS/article/viewFile/631/534
10. http://ndt.oxfordjournals.org/content/24/8/2428.full.pdf+html

Backup Calculations

C_0 is 3.3 pg/mL according to [5]. If the average blood vessel size is taken to be $1mm^2$, then the 1-dimensional concentration becomes C_0 = ($1mm^2/1cm^2$) 3.3 pg/mL = 0.033 pg/cm.

There are 1,000,000 glomeruli, with an average volume of 10^7 um^3 [9,10]. This gives a total volume of 10^{13} um^3 which is 10mL. This means that the rate of absorption R must be 7.5 mL / 10 mL / 60 seconds = 0.012 1/sec if we use the rate of excretion from [5].