Adaptation in Molecular Communication Survey

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1 Introduction

[Nakano et al., 2013] [Akan et al., 2017] [Akyildiz et al., 2008] [Kuscu and Akan, 2016] [Kuscu et al., 2019]

1.1 Molecular communication examples

Molecular communication is the most promising communication paradigm for nanonetwork communication inspired by already existing biological communication between nanoscale living entities in nature such as human body. In nature, numerous molecules are used as information molecules in order to transmit and receive information for functionality. [Koca et al., 2021] Most important examples of molecular communication systems can be observed in human body. Throughout the human body, infinitely many information molecules are communicated between transmitting and receiving systems in order to function in a perfect harmony in integrity.
Many ligands in olfactory systems act as information molecules that modulates signal pathways in gustatory and metabolic control systems. It is observed that there is a communication between olfactory sensors, gustatory sensors and metabolic control systems. All communication is realized using information molecules, ligands, that are detected and sensed by different type of receptors, which activates another signaling pathway in different system. The list of ligand types, receptor types and signaling pathway can be available in [Martin et al., 2009]. [Murat hocaların olfactory paperina referans verilebilir]

G-protein coupled receptors(GPCRs) are large group of cell surface proteins that detects an input information molecule and activates cell signaling pathways using G proteins coupled with receptors via conformational change due to the ligand binding. GPCRs spreading throughout the body involves in numerous physiological roles. There are thousands of ligands binding to gpcr type receptors in human body and nature.[Pándy-Szekeres et al., 2017, Munk et al., 2016] Each binding controls a physiological process. The processes modulated by GPCRs function in visual, gustatory and olfactory sensory systems[Rosenbaum et al., 2009], behavioral and mood regulation [Watkins and Orlandi, 2020, Grammatopoulos, 2017,

Catapano and Manji, 2007], regulation of immune system activity and inflammation [Lämmermann and Kastenmüller, 2019]. As an example of GPCRs, Beta-2 adrenergic receptor which binds to epinephrine is well studied. [Johnson, 2006] When primary endogeneous agonist epinephrine binds to beta-2 adrenergic receptor, combined signaling events occurs and results physiological responses such as smooth muscle relaxation, glucose synthesized from glucogen in the liver and increased perfusion and vasodilation. Adrenaline hormone, secreted by adrenal glands, acts as an information molecule and is detected by the receivers beta-2 adrenergic receptors. The detection results series of physiological responses in the body.

INSULIN METABOLISM When regulating blood sugar level, many hormones are used as information molecules including insulin. When insulin secretion is increased, insulin receptors are activated. Insulin receptors are tyrosine kinase type receptors, hence triggers autophosphorylation process and corresponding signaling pathway, that activates glucose transporter taking blood glucose into the cell and trasforming it to glycogen. Insulin receptors are distributed throughout the body, especially in liver, muscle tissues, adipose tissues. In this regulation mechanism, pancreas(transmitter) communicates using insulin as an IM(information molecule) in order to activates intracellular glucose-glucogen transformation in the target cells(receivers), hence to reduce blood glucose level.

GABA, benzodiazepines

Neuron cells communicate through neurotransmitter molecules and ion channels. Although the whole process is a very complicated interwoven control systems, neurotransmitter transmission affects the activation status of the target neuron and on/off status of the ion channels affects the neurotransmission process. To exemplify a molecular communication process, we can observe the relations between GABA and its receptors' allosteric modulators benzodiazepines. [Morlock and Czajkowski, 2011] When a benzodiazepine is taken externally, it binds the GABA receptor allosterically and up-regulates GABA binding, ie increases the effect of GABA on ion channels. Thereafter, increasing Cl ions in the neuron cell decreases the firing activity of the neuron. [Walters et al., 2000] As neurons uses neurotransmitters as IMS for intercellular communication, benzodiazepines, among with other psychoactive drugs and psychiatric medicine, can also be used as IM externally to communicate with neuron cells. [Roy-Byrne, 2005]

1.2 Adaptation of Living Systems

Fluctuating and dynamic properties in the nature yield highly improved adaptation mechanisms in the living cells. Throughout the years, the researchers have been tried to understand cell adaptation mechanisms by exploring fundamental behaviors such as bacterial chemotaxis. It has been discovered that

there are many adaptation mechanisms implemented by cell membranes, ligand receptors and intracellular signaling mechanisms. Cell membranes and receptors have evolved in order to realize fast and reliable communication and higher information capacity.

Cell has developed more than one receptor for a single or multiple ligand types in order to increase its information coding capacity. By increasing the receptor types increases the response range and concentration coding capacity of the cell. [Getz and Lánsky, 2001] This adaptation mechanism improves concentration coding capacity and efficiency significantly. For the maximum coding efficiency, it is showed that multiple receptors(receptors with different dissociation constants KDs) must be implemented with symmetrically placed dissociation constants KDs through the concentration range.

Another example of developed adaptation mechanisms is due to background noise. Background noise can cause receptor operating in saturation region yielding decreased sensitivity. For a basic bacterial property such as chemotaxis, a bacteria cell needs to preserve its sensitivity to the ligand concentration even in the background noise. Otherwise, bacteria cannot dissociate and response different ligand concentrations and not implement chemotaxis behavior. In order to preserve sensitivity in the background noise existence, it is demonstrated that cells improved adaptive mechanisms such as dynamic, tunable receptors(tunable dissociation constants KDs).[Mello and Tu, 2007] Dynamicity and tuning of dissociation constant KDs are implemented by either allosteric control mechanisms or controlling/adjusting receptor methylation level.[Olsman and Goentoro, 2016] Allosteric control of receptor dissociation constants allow cells to preserve its sensitivity to ligand concentration in the presence of background noise. It prevents the receptor operates in the saturation region. Receptor methylation level also directly affects the receptor response(KDs), and can be adjusted by some intracellular signaling networks.

[Olsman and Goentoro, 2016] Another mechanism developed in cells throughout years in order to improve sensitivity is cooperativity. While heterotropic allostery shifts receptor response curve, cooperativity behavior changes and steepens the reseptor response curve. As in Hemoglobin-Oxygen mechanism, some receptors have ability to bind multiple molecules each also allosterically facilitate the next binding process. This cooperative behavior using multiple dimers as homotropic allostery results improved sensitivity.

[Kirby et al., 2021] [Lan et al., 2011] states that both local and global receptor adaptation mechanisms are implemented by cells. As locally, a binding changes its receptor's methylation level, globally receptor crosstalk behavior [Carballo-Pacheco et al., 2019] propagates the adaptation through the membrane receptor cluster. Both mechanisms aim to maintain high sensitivity even in complex environments.

1.3 Why adaptation is required in molecular communication (brief summary of Section 3

In molecular communication, due to stochasticity in nature, there is a lot of interfering sources, noise, turbulence that can affect the communication performance adversely. For example, there may be a background noise that is an external ligand receptor interfering molecule may coming from one of many different sources. While same IM molecule or an agonist molecule exists in the communication medium as a background noise, it can shift the operating region towards the saturation regime of the receptor response curve, decreases sensitivity and therefore deteriorates communication performance.

For one-to-one single transmitter single receptor communication, due to imperfectness of the channel response, there exist intersymbol interference(ISI). Intersymbol interference also shifts the receptor response curve towards the saturation regime by increasing total concentration, decreasing sensitivity and communication performance. Other than ISI, stochasticity due to mobility also brings stochasticity in bit concentrations. While transmitter and receiver are approaching each other, it increases ISI, otherwise it decreases ISI. It certainly affects the optimum KD by shifting the operating regime towards sparsity or saturation regime. Moreover, a degrading enzyme in the channel affects the concentrations and ISI. It can shift the operating region towards the sparsity regime of the receptor response curve and demolish sensitivity.

Off-state leakage is also another reason that makes bit-0 concentration approach towards bit-1 concentration and increases required sensitivity for the same communication performance. Furthermore, stochasticity in molecule generation process in transmitter also affects bits concentrations, brings and additive noise on bit concentrations. All source of stochasticity and interferences highly possible affects the communication performance significantly.

For multiple link communication systems, another communication source can interrupt the communication, causing multi-user interference. Multi-user interference is another source of interference causing the change in sensitivity and performance. To deal with this stochastic nature and turbulence in the environment, we need to use adaptive mechanisms in order to preserve and increase communication performance, as living systems already evolved to do that. As already observed in nature, there are numerously discovered and undiscovered adaptivity mechanisms implemented by cells. One of the most important part of adaptation is implemented using ligand receptors. Allosteric regulation of the single receptor response curve, cooperativity, adjusting methylation level, synthesizing auxiliary different ligand receptor, using more than one recep-

tors(different receptors with different response curves, KDs), receptor crosstalks, receptor clustering are some of the important mechanisms implemented by cells via ligand receptors. From molecular communication perspective, using ligand receptors and regulation of receptor response curves and sensitivity can be most promising adaptive mechanism. Due to advances in synthetic biology, design, generation and synthesis of ligand receptors and regulation of their response curves and sensitivity is easier to implement than realizing complex intracellular signaling nanonetworks.

2 Natural Receiver Adaptation Mechanisms

2.1 Heterogeneous Receptors

Cells generally do not have single type/homogeneous receptors expressing one ligand. It has been observed that in most cases, many ligand molecules do have affinity with more than one ligand receptor. More than one type or heterogeneity here refers due to that the main discrimination is on ligand receptor binding/unbinding rates and receptor dissociation constant. Different dissociation constants mean different receptors, heterogeneity. The reason behind that the cell membrane expresses heterogeneous receptors for a ligand has been being explored.[Getz, Lansky Receptor Dissociation Constants] It is understood that the main reasoning behind this adaptation is to preserve sensitivity over expanded ligand concentration range. It is a basic adaptation mechanism of a cell to a volatile, extended concentration range. Information theoretically, this also means concentration coding efficiency. To get maximum coding efficiency, for a uniformly distributed concentration, a cell must synthesize ligand receptors such that their dissociation constants are symmetrically replaced over the ligand concentration range. This replacement gives a linear response over the concentration range. By synthesizing another receptor with different dissociation constant also means to increase responsive ligand concentration range. When ligand concentration has a variance due to some volatility, turbulence, noise, having more than one receptor types prevents the cell to operate towards saturation or sparsity regime of ligand receptor response curve, hence to preserve sensitivity for extensive concentration range. (In [Getz and Lánsky, 2001], for a uniformly distributed ligand concentration, it has been demonstrated that symmetrical replacing of KDs results maximum coding efficiency.) With homogeneous receptors, the response curve expresses 4-fold ligand concentration, ie linear response(preserving sensitivity) over 4-fold concentration. Since, ligand concentration range is greater than 4-fold in real life due stochasticity, cell membranes evolved to adapt to express extensive ligand concentration range. For homogeneous case, if the ligand concentration is below than 4-fold range, it implies that the receptors operate in sparsity regime and sensitivity is very low. Low sensitivity inhibit the cell to observe concentration changes and basic activities such as bacterial chemotaxis. Similarly, when a ligand concentration is above 4-fold range, the homogeneous receptors operate in saturation regime,

that results very low sensitivity. Thus, in order to preserve vital operations, cells are adapted to express extended range and preserve sensitivity over ligand concentration range by exploiting heterogeneous receptors. [RESİM 1,2,3,4 reseptörlü response curve]

2.2 Allosteric Regulation-Heterotropic Conformational Modulation of Receptors

Ligand receptors are complex tangled proteins. Ligands bind the receptors resulting conformational change and chemical proteins. Receptors are not generally specific to one ligand. They tend to have more than binding sites for multiple ligands. Allostery is one of the most important properties of proteins. The term "Allos means "the other" and the "allosteric side" means "the other, or distant side". Allostery is a biochemical process that binding allosteric site of a ligand receptor causing conformational change in protein structure and altering the ligand receptor bounding properties. [Hacisuleyman and Erman, 2017]

Hence, a protein's ligand receptor binding proteins can be regulated by allostery, also known as allosteric regulation. Allosteric regulation often involves a biochemical substance different than the ligand, that is able to bind different sides of receptor protein. If allosteric modulation is realized by different substance than ligand, it is calle heterotropic allosterism. It does not involve any cooperativity, ie for multiple dimers one ligand binding fascilitate the next binding by homotropic allosterism. It is different than homotropic allosterism, where ligand binding site can also be an allosteric site, that ligand binding act as an allosterism. Whereas cooperativity steepens the ligand response curve, heterotropic allosterism merely shifts the response curve.

RESİM KAYDIRMALI RESPONSE CURVE

One of the main classical models explaining allostery is Monod-Wyman-Changeux model described in 1965(?). For heterotropic allosterism, when an allosteric substance binds to the receptor protein, it either fascilitates ligand binding, ie shifts the response curve left, or deteriorates the ligand binding, ie shifts the response curve right.

This adaptation mechanism is mainly used to tune the receptor's dissociation constant to its optimum(considering background noise). Specifically, when a higher concentration background noise is introduced, receptor response curve can be tuned right. When the background noise lowers, the receptor response curve can be retuned left. By allosteric regulation, it is possible to tune the receptor response curve almost without changing the curve behavior, preserving sensitivity. Tuning response curve avoids saturation or sparsity.

2.3 Cooperativity-Positive Catalytic Homotropic Regulation

Sometimes, ligand receptors do have more than one ligand binding sites, ie 2,3,4 ligands can bind the same receptor. Most famous example for this behavior is that hemoglobin molecule having four subunits can bind 4 Oxygen molecules. Ability to bind more than one ligand brings an important advantageous adaptation mechanism:cooperativity. Cooperativity means that each ligand binding behavior is affected and facilitated by previous ligand binding and present conformation or state of the receptor protein, resulting cooperative binding behavior. Binding one oxygen atoms resulting a conformational change in the hemoglobin molecule that yields the other binding sites can bind an oxygen molecule easier. In other words, oxygen binding sites are also allosteric sites for other oxygens(homotropic allostery). This cooperative binding behavior brings steeper, sigmoidal shaped ligand response curve. Moreover, there is a trade-off between dynamic response range and sensitivity. Steepening the response curve increases sensitivity around linear operating region, causing linear range shrinks and shape turns sigmoidal.
RESİM-COOPERATIVITY SIGMOIDAL RESPONSE SHAPE

3 Molecular Communication Scenarios

3.1 Background Interference

One of the most common interference is background interference which is independent from the information molecule. In this scenario, the transmitter communicates with the receiver using an information molecule. The receiver senses the information molecule using its ligand receptors. The ligand receptors have binding affinity with the information molecule and response curve summarizes the binding behavior. In the background, there is an external molecule that has nonzero binding affinity with the receivers ligand receptors. The background molecule disrupts the original receptor ligand response curve and thus the communication performance. When the interfering background molecules bind and activate ligand receptors, ie agonism, it can shift the ligand response curve upward. Therefore, the receiver operates in the saturation regime. In the saturation regime, the ligand receptors sensitivity, ability to discriminate zero-bit and one-bit concentrations over noise, is significantly low. Hence, operating in saturation regime significantly deteriorates communication performance. If the interfering molecule is different and behaves antagonistically, ie binds and deactivates the ligand receptors, then the response curve is shifted downward and the sensitivity is decreased in the linear regime. In this case, the receiver operates in the sparsity regime.
In both scenarios, in the existence of a background interfering molecule, the receiver needs to adapt in order to preserve its sensitivity and avoid from saturation or sparsification. The most important adaptation mechanism for the

receiver is the modification of its dissociation constant, the ratio of the ligand binding/unbinding afinities and the response curve.

3.2 Intersymbol Interference

We consider single-to-single communication link. In molecular communication, the channel is biochemical medium and the main transportation mechanism is mostly diffusion. When molecules are released from transmitter, they are transported via diffusion and drift in a biochemical medium and at the receiver, as an channel output response, we observe a concentration of the information molecule. As a result, impulse response is not an impulse, it has dispersion,ie smoothed impulse response due to diffusion. The dispersion and fading in the channel causes intersymbol interference, ie convolved concentration as constructive interference. Expected ISI increases the zero-bit concentration and 1-bit concentration and results that the receiver operating region shifts toward saturation region of the response curve and decreased sensitivity. Due to increased expected concentration levels, the receiver needs to adapt its response curve for the new concentration levels, ie can shift its response curve right by increasing its dissociation constant. For homogeneous receptors, adaptation can be yielded merely by adjusting dissociation constant and shifting the response curve horizontally. This modification can be realized biologically by allosterism. For heterogeneous receptor cases, one of the possible adaptation mechanism is introducing new type of ligand receptor, ie ligand receptor with different dissociation constant. In this scenario, half-occupancy concentration of the new adapted heterogeneous receptors is geometric mean of the dissociation constants(when the number of receptor types are equal). Hence, the receiver adapts itself with introducing new receptor type with different dissociation constants, shifting the center of the response curve. In this heterogeneous scenario, however the sensitivity in the center(half occupancy concentration) is lower than the homogeneous case due to broadened response range.
Consequently, the receiver needs to adapt its response curve for the new concentration levels increased by ISI. There are different adaptation mechanisms which the receiver can apply by modifying its ligand receptors.

3.3 Imperfect Molecule Generation Process in Transmitter

In this scenario, we consider the imperfections in the molecule generation process in the transmitter. We model start of the transmission as instant release of the information molecules from the transmitter. Realistically, instant release is not possible and the transmitted signal is not an impulse. Hence, more smoothed version of the impulse response is generated from transmitter towards receiver. Only smoothing in the generation process cause dispersion in the output response, hence increased ISI. Increased ISI requires adaptation. The receiver needs to adjust its response curve according to the increased ISI.

3.4 Multi-User Interference

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