GPCR's – The Lingua Franca of Cellular Logic

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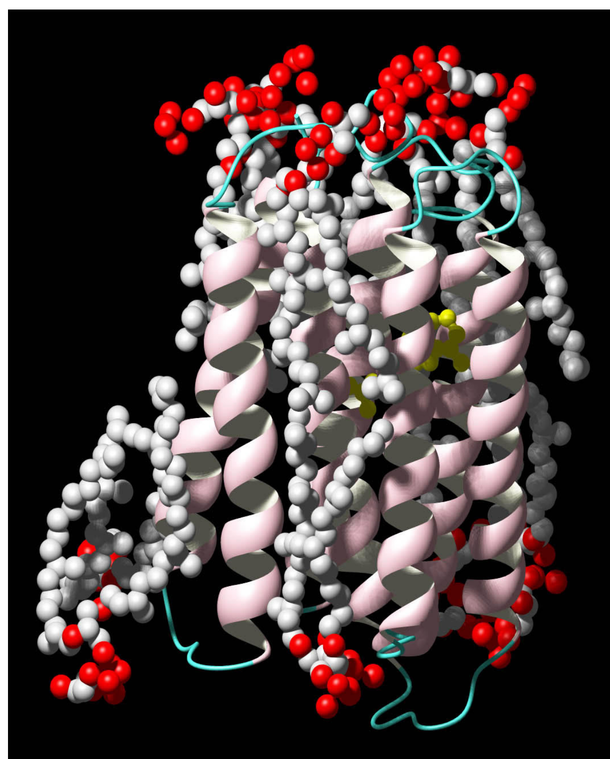
Abstract

GPCR's: G-Protein Coupled Receptors targets and their cognate ligands constitute 1/3 of the drugs used to treat various disorders, from cancer, to intestinal disorders, to mental illness. These ligands range from photons in the case of rhodopsin, a key protein in vision, to the Her2Nu growth factor receptor, itself the topic of an entire book, by Robert Bazell, professor at Yale and NBC Science Correspondent. With a myriad of functions serving the communication needs of cells of over 200 types, they bear similarities which lend themselves both to Linnaean cataloging and functional simulation. A complete map of their definition and interaction has yet to be developed although a number of efforts have begun that process [1, 2, 3, 4]. Enabling a detailed visualization of GPCR interaction is not a mere academic curiosity. It would be as useful for the student, scientist or physician as a world atlas or Google Earth™ is to those with geographic questions.

Introduction

G-Protein Coupled Receptors are a principal communication and signaling mechanism between cells. These "semaphores of the cell" are anchored firmly in the cell wall by a barrel shaped bunch of seven corkscrew protein structures called the transmembrane spanning proteins. Each GPCR sits in the cell wall exposing an external component to potential signaling molecules in the extracellular environment. Each GPCR also presents an internal component to cytosolic machinery within the cell, that can trigger small or large changes, including downstream signals that penetrate the nucleus and trigger cell division.



Rhodopsin GPCR - Courtesy Dr. Steven Fliesler

According to the NIH: " FDA-approved drugs target at least 108 GPCRs, with an additional 66 receptors targeted by agents in clinical trials. The FDA-approved drugs constitute a US market of 180 billion dollars annually.

GPCR Targets

British National Formulary drugs that target GPCRs include analgesics, opioids, antidepressants, antihistamines, beta blockers, bronchodilators, gut motility, diabetes, Parkinson's, psychoses, addiction, hormones and tumor suppressors in cancer and glaucoma. Thus, understanding GPCR's is important for wide variety of human and animal health concerns.

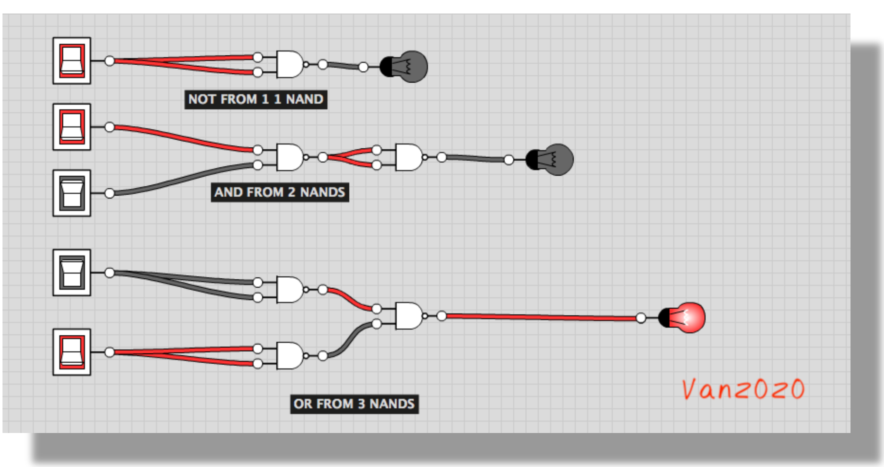
Candidates for Abstraction

They also serve as an ideal candidate for mathematical abstraction for functional analysis, for pathway exploration, for *in silico* diagnostics, for bioinformatic assays and computer-aided drug search. What I mean by 'abstraction' will be covered in a moment. First a brief, but necessary digression.

Cellular Logic and Digital Codes

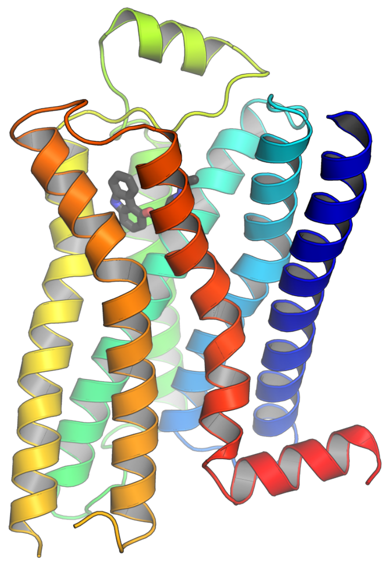
Since we are talking about cellular logic, we should take a moment and observe that all life on Earth is facilitated by a base 4 digital code, in the form of RNA, and DNA. The underlying informational architecture of every plant, animal, insect, virus and bacterium is based on a code that can be replicated, mutated, and selected by environmental pressures that confer survival advantages. I want to drive home just how profound the digital aspect of this is, and how life, at its root, is a form of asynchronous, distributed, parallel computation. Alan Turing showed that all deterministic computation can be represented as an abstract machine, called a Turing Machine, that represents information using two symbols, strung sequentially together on an abstraction called a "Turing Tape". These two symbols represent a noiseless yes or a no, true or a false. Nature has chosen a closely related base 4 code, requiring four states which can be represented as exactly two binary symbols.

Symbols, Signals, Gates and Noise



All Three Gates can be made from NAND Gates

In all of communication as J.R. Pierce has written, there are signals, symbols and noise. George Boole gave us Boolean algebra and the fundamental logic gates of AND(a,b), OR(a,b), and NOT(a). AND & OR are binary operations, NOT is a unary operation. It turns out that any of these primitive gates can be constructed using a single type of gate, NAND(a,b) which is also a binary operator.



The human beta-2 adrenergic receptor in complex with the antagonist carazolol.

GPCRs all share a single central stable structure: seven membrane-spanning helical domains.

In contrast, according to Kobilko et. al. "GPCRs are no longer thought to behave as simple two-state switches. Rather, they are more like molecular rheostats, able to sample a continuum of conformations with relatively closely spaced energies."

Redundancy Facilitates Fault Tolerant Design

At the cellular n biological systems there are overwhelming levels of redundancy, so that if one cell is damaged, another can readily take its place. The same is true for GPCR expression where individual receptors are either recycled to the cell surface or marked for destruction via the ubiquination pathway. In traditional computing software, redundancy is avoided to 'save space'. This contrast between redundancy and minimalism between natural and manmade computing systems is an interesting distinction and possible clue for the future of computer architecures. The GPCR relevant part is that there are multiple instances of GPCRs constantly being expressed and recycled on the cell surface.

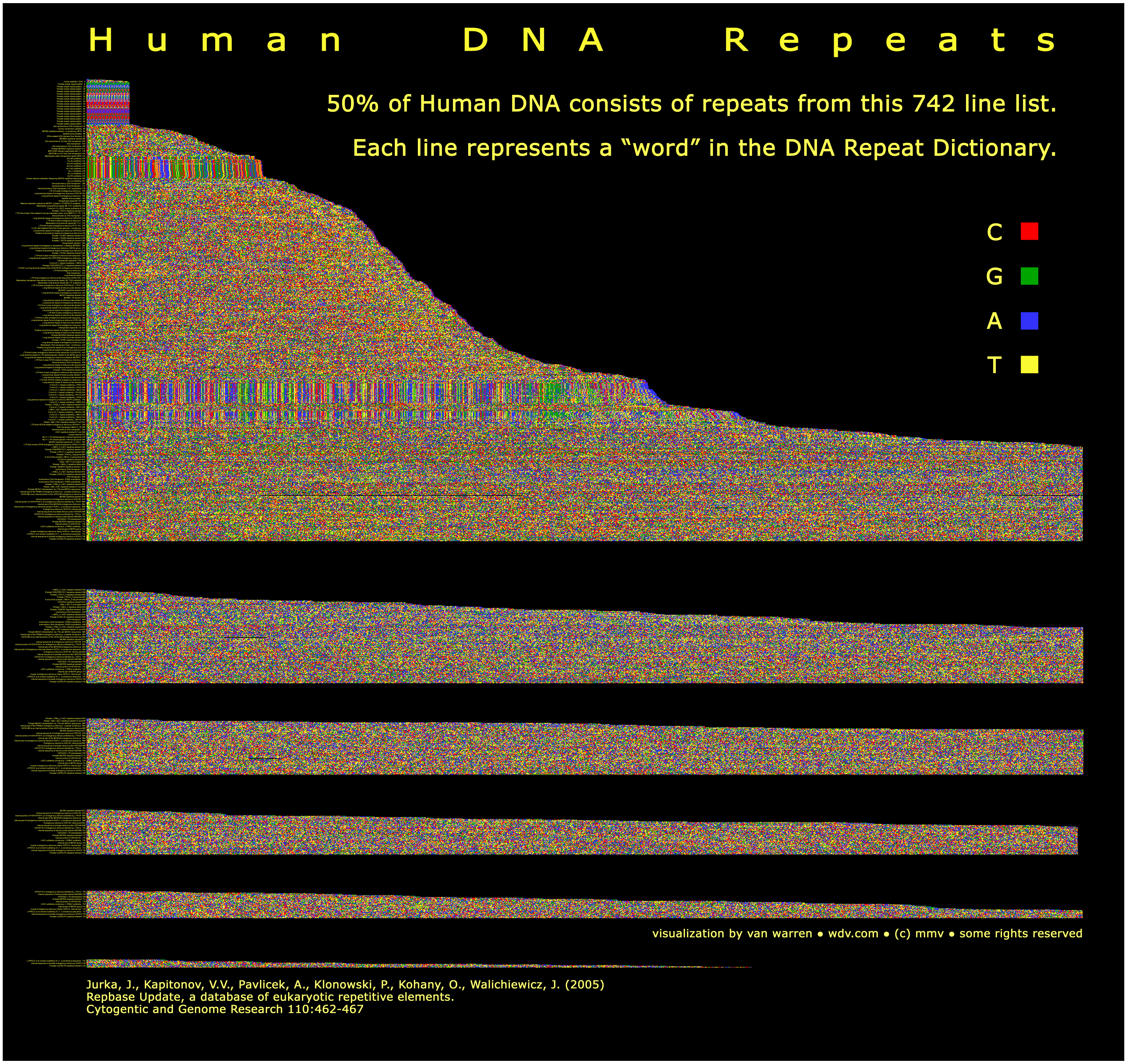
The Ultimate Packaging Solution

Moore's Law articulated in 1965 by Gordon Moore of Intel states that about every two years that computers double in speed or halve in price. This observation which has been accurate for the past 55 years is a consequence that the circuitry comprising computer gates have continued to shrink, such that, at this writing, these features are about 7 nanometers wide. Moore's Law is thus a consequence of the shrinking of the package while its information density increases.

Compounding the astonishing miracle of life is the packaging of DNA. With the exception of circulating red cells who have expelled their nuclei in favor of increased payload, each of the ~37 trillion cells in our bodies contains 2 meters, or about 6 linear feet of DNA, coiled on protein spools called histones, that aggregate in supercoiled structures to fit in packages less than 10 microns wide. The packaging feat is further compounded when one considers that only a single cell is required to specify all the architectural information for each unique human being.

Evolution of Computing, Evolution of Life

The evolution of computing machinery and the evolution of life on Earth have taken considerably different approaches. Computing machines as we have known them started as sequential von Neumann machines, executing instructions one a time, with concurrency appearing later as multiple processors and now multiple 'cores' on a single processor. Life appears to have used concurrency from the start, a notable example being viruses that show their influence by performing one singular activity – copying themselves. Both life and von Neumann hardware can be viewed as computing machines. Viral wreckage and other repeats comprise 50% of our genome, making one wonder what would happen if it was, "cleaned up".



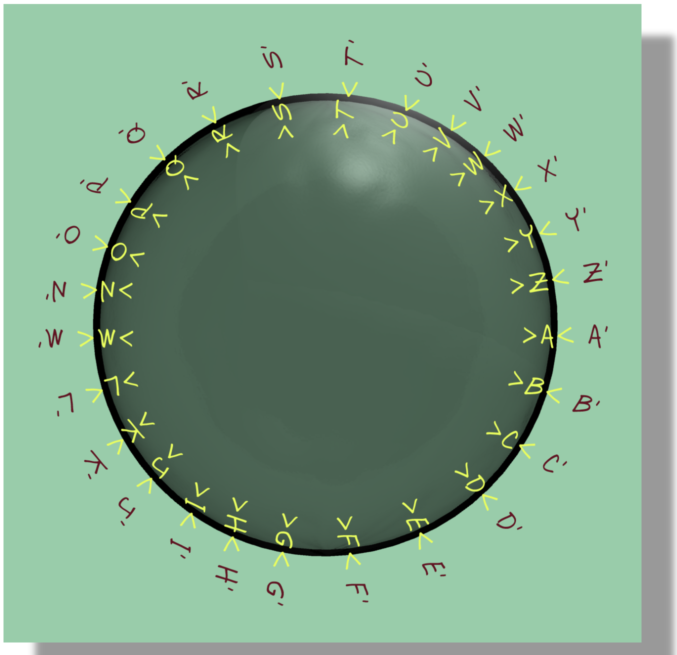
Human DNA Repeats from short to long, visualized by the author

Computer Viruses

Computer viruses work like their biological counterparts. A significant milestone in modern computing was reached when one computer could infect another with a set of instructions whose only goal was to make another copy of itself.

GPCRs in Situ

Eukaryotic or nucleated cells of higher life forms use specialized surface receptors, like the GPCR's to determine which messages that they receive. Each receptor-specific message activates a unique function determined by the architecture of that receptor. As such receptors are the gateways, the *logic gates* mediating cellular activity.



Receptors and Ligands

Consider a cell surface studded with receptors as in the figure to the left where:

- A-Z are different receptor types
- A'-Z' are different ligand types
- Each R-R' pair has its own binding energy.

If the binding energy is on the order of the surrounding energetics, we might presume the docking is reversible. If a ligand binds irreversibly, then its binding energy is much higher than its surroundings.

When A' activates its receptor, it is called an 'agonist'.
When A' inhibits its receptor, it is called an 'antagonist' or 'inverse agonist'.

Constitutive Activity

A receptor which produces biological response in the absence of a bound ligand is said to display "constitutive activity". The constitutive activity of a receptor may be blocked by an antagonist.

The Small Molecule Currency of Biology

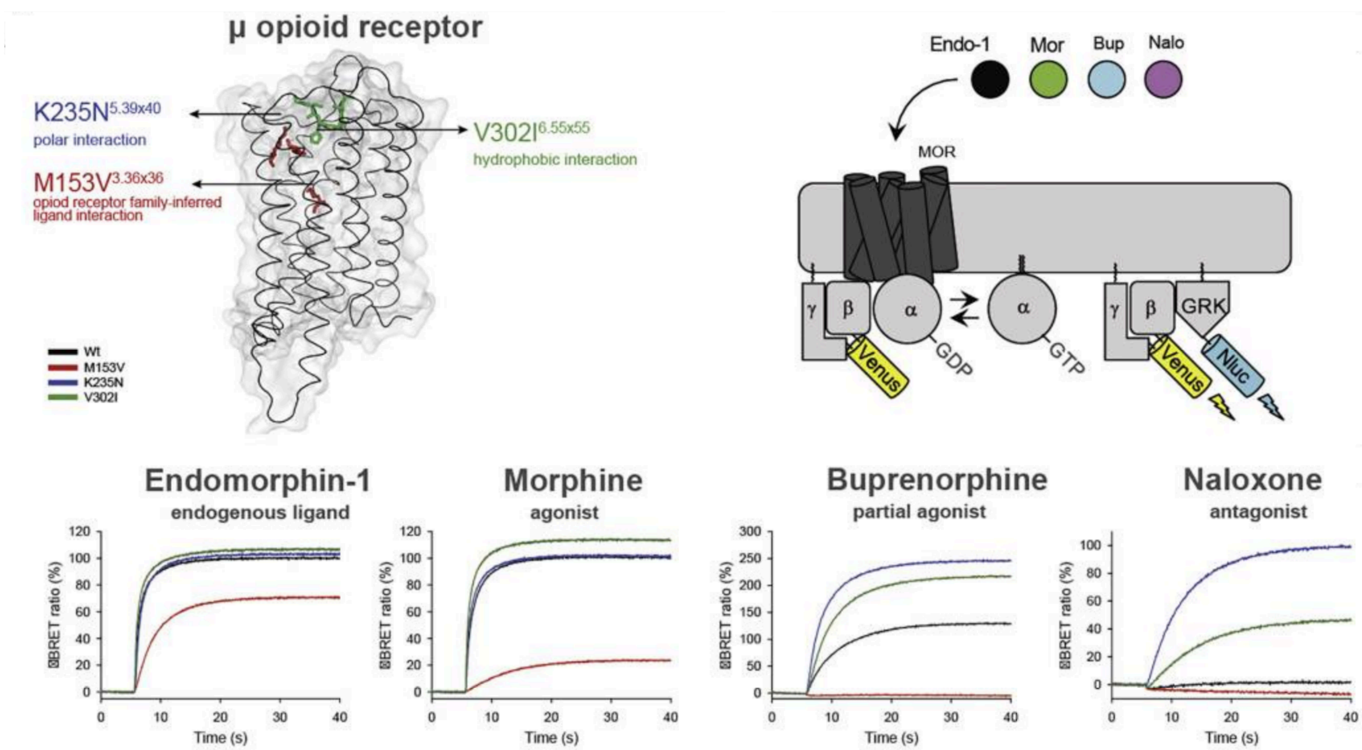
Messages typically consist of small molecules, hormones and neurotransmitters that act over both short and long distances. Messages can also be larger molecules and proteins as in the case of epidermal growth factor, the ligand of the Her2Nu receptor. Whether the message is small or large these cellular networks carry the burden of managing the complex traffic necessary for the maintenance of life.

A Bioinformatic Mandate

Here we encounter our first mandate: Simulate the communication traffic of the GPCR receptors for specific cell types to understand disease processes, mechanism and normal cell function.

Mapping Pathways

It is because of these communication pathways that life exists. Each receptor is part of a pathway, both intracellular and extracellular. Many of these pathways have been mapped and visualized, some have not. These pathways span both cell types and organ types - moving quickly between these hierarchies of scale is a critical aid to understanding. Imagine that, in the future, a one could have a "personal receptor mapping" diagnostic procedure. This would facilitate optimal dosing, and optimal drugs/ ligands factoring in each individual's personal. As an example, consider the four responses from four opioid receptor types:



Varying 'Personal' Opioid Receptor Responses – Excerpted from Figure 5 Here

Elucidating these pathways and understanding what happens when they go wrong has exploded since the sequencing of the human genome.

Receptors and Ligands as an Algebraic Language

It is essential that we recognize that the receptors and ligands form nothing more and nothing less, than a language of communication whose rules can be codified, explored, simulated and "modified for correctness", the latter phrase being the root of the multi-billion-dollar pharmaceutical industry. Besides providing descriptive nomenclature I wonder if we can make these molecular signaling pathways resemble traditional spoken and iconic languages for enhancing both our interaction and our understanding of them.

Wrapping up this digression, GPCR's form a significant chunk of the logic that cells use to communicate. Understanding the language of GPCR's is thus a worthwhile activity.
My late colleague Marilyn Fulper referred to this language as, "the Handwriting of God".

Abstraction By Example

Returning to the main thread; What I mean by 'abstraction' is best illustrated by an example. Even though the receptor is a complex 3D structure, we can create a 2D analog that communicates the essential aspects of its function. In the figure below, the input of the GPCR is on the left, where an incoming photon triggers a conformational change in the output segment on the right, signaling the arrival of said photon.

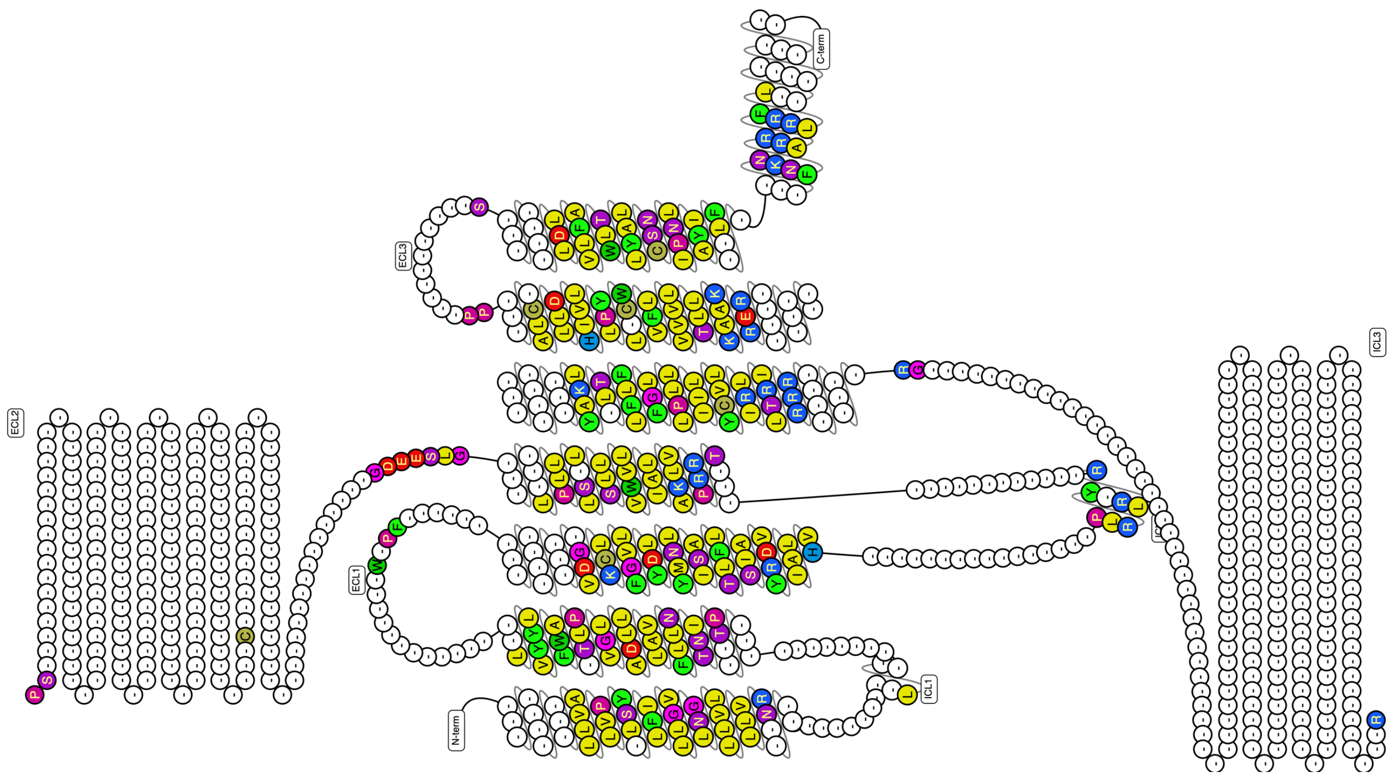


Figure - Human Rhodopsin - Courtesy GPCRdb

The GPCR Economy

To understand this busy economic system of currency exchange within biological cellular networks we must consider GPCRs:

1. Equivalence to Computational Engines
2. [Five Families Each with Three Functional Segments]()
3. External Interaction
4. Internal Interaction
5. Cell Surface Interaction as in GPCR dimerization
6. [Synthesis from Specific Genes in Specific Locations]()
7. [Gene Expression Regulation]()
8. [DNA sequence of Wild Type and Mutant]()
9. [RNA sequence]() between Genotype and Phenotype
10. [Amino acid sequence]() – Wild-Type and Mutant
11. [Folding and Chaperones]()
12. [Trafficking & Deployment]() – Synthesis to Cell Wall

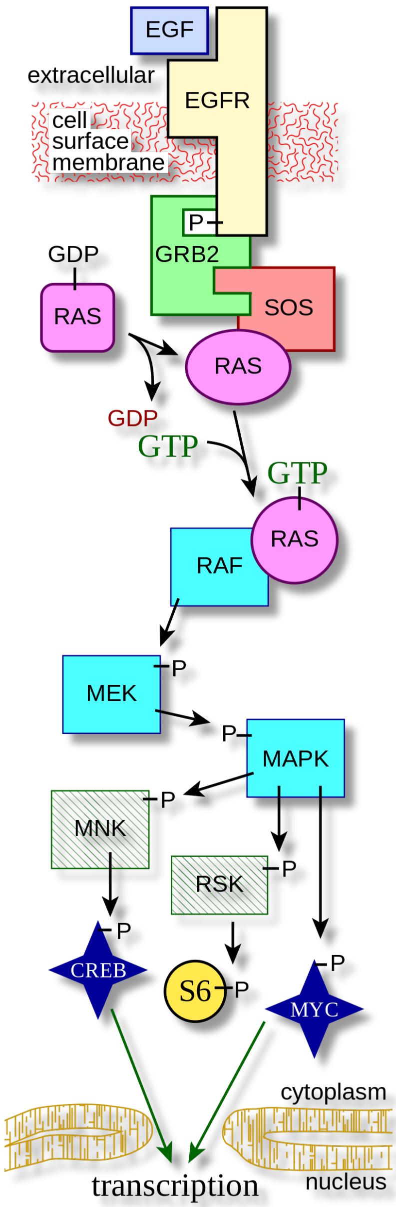
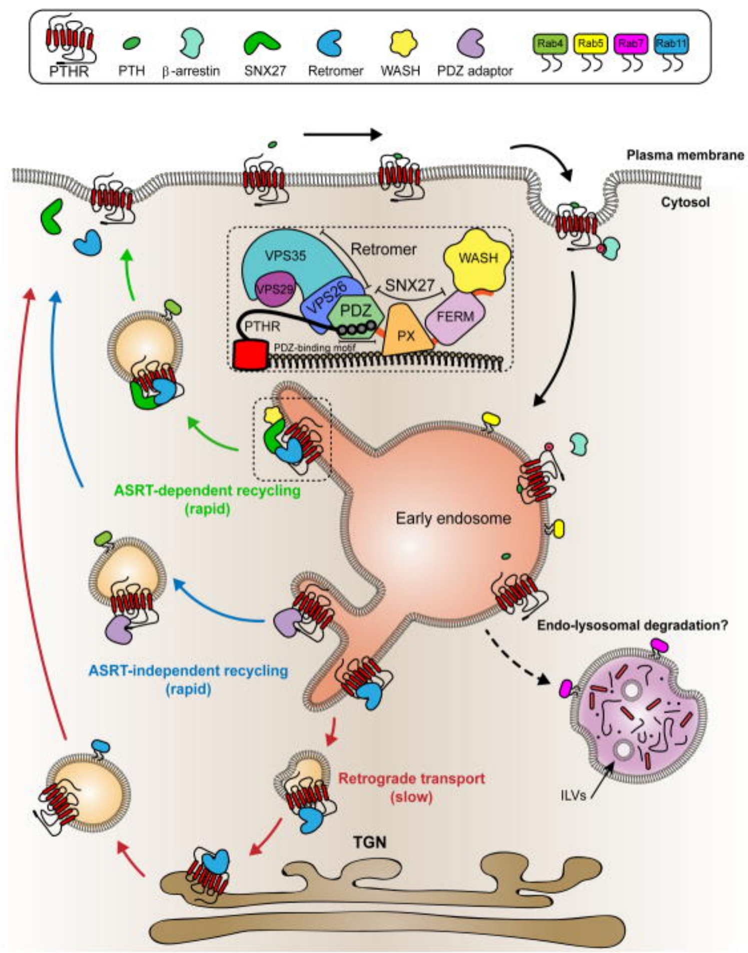


Figure – Her2Nu / EGFR receptor



GPCR Signaling and Trafficking: The Long and Short of It

Computational Equivalence

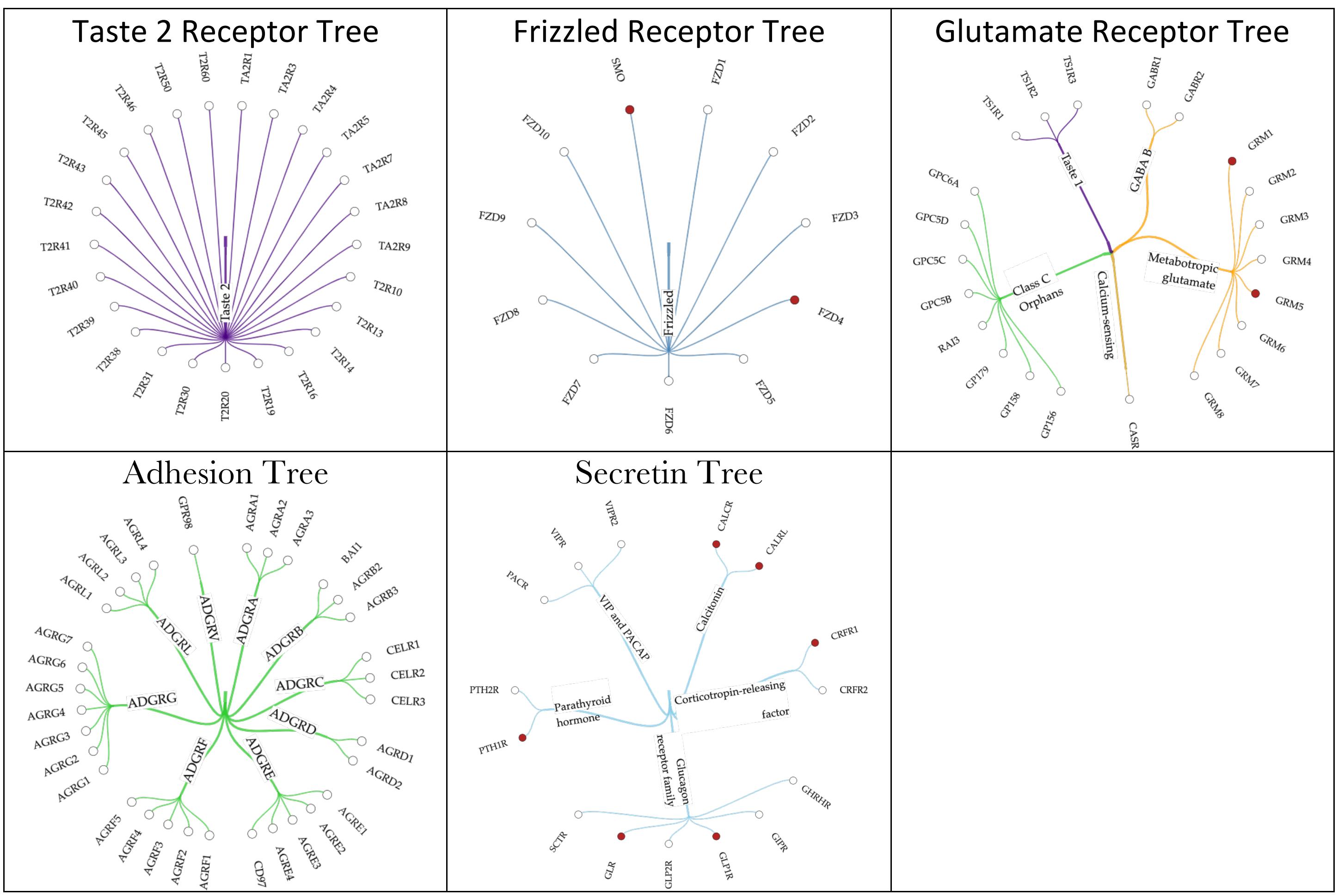
Each cell of the over 200 cell types in humans can be viewed as a computational engine. Cells interact with the outside world via several mechanisms. Significant among these are the GPCR's. Each GPCR instance bobbing in the cell wall is a molecular switch, a chunk of logic, a gate that can be activated that causes a change of state within the cell. Cell activities themselves driven by a base four equivalent Turing tape are subject to transcriptional noise and errors through wobble and other mechanisms.

Five Families In Vertebrates

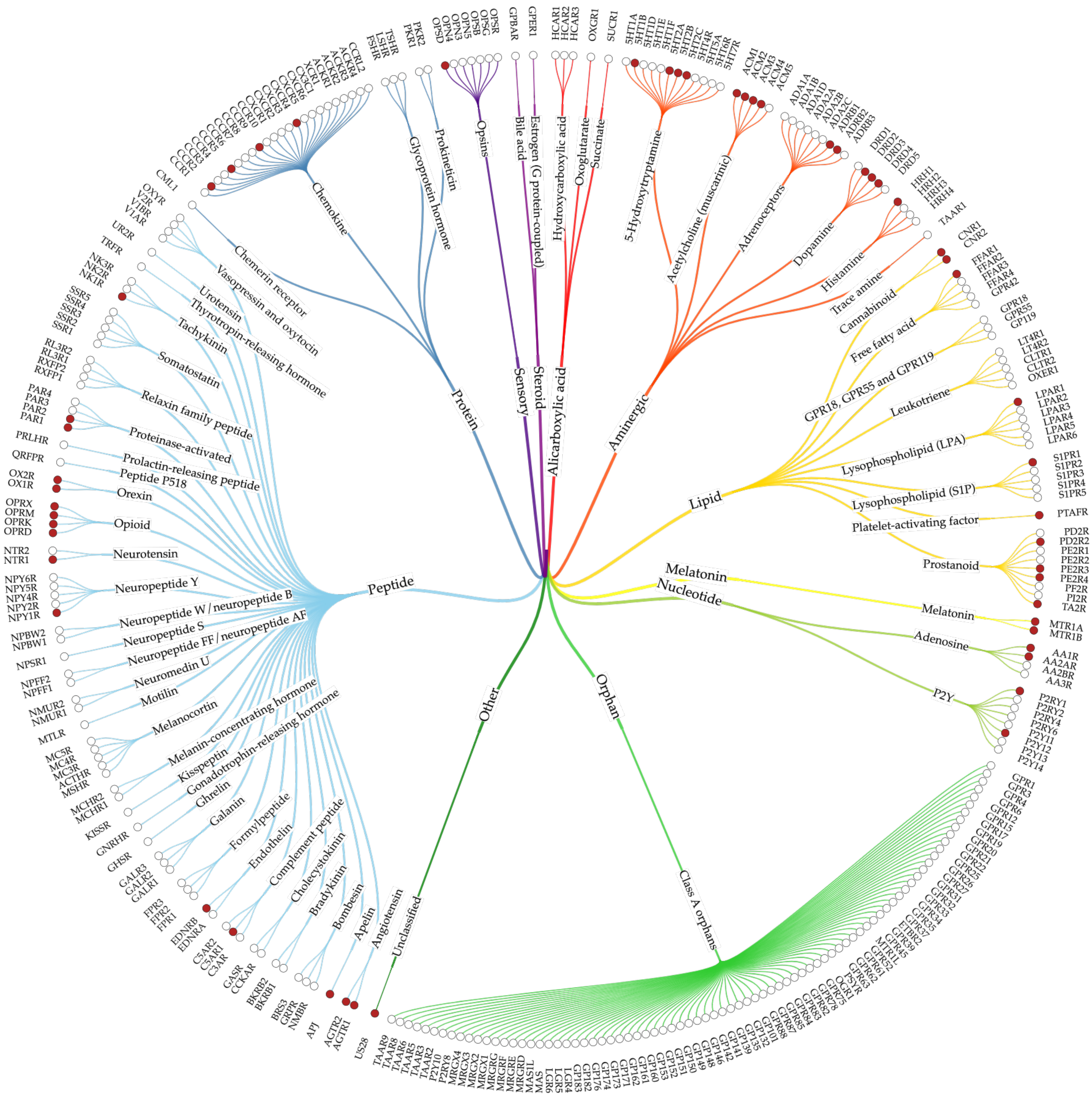
GPCRs in the gpcrdb.org database are divided into six classes by sequence and functional similarity:

- Class A: Rhodopsin
- Class B1: Secretin
- Class B2: Adhesion
- Class C: Glutamate
- Class F: Frizzled
- Taste 2

The Inventory of GPCRs (for which crystal structures exist)



The rhodopsin family is by far the largest and most diverse of these families. The following graphic from gpcrdb.org shows their functional decomposition. For each terminal node, there are many variants. These receptors are not a full count, since there are orphan receptors and receptors that have not yet been crystallized and studied via X-Ray spectroscopy.



Rhodopsin GPCRs

The Noisy Parts

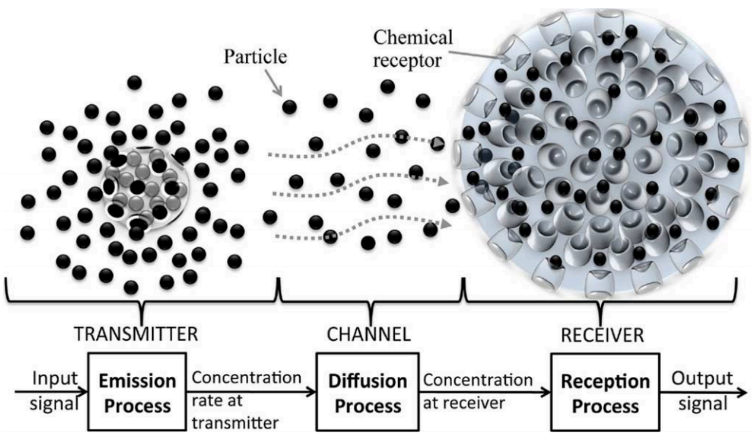
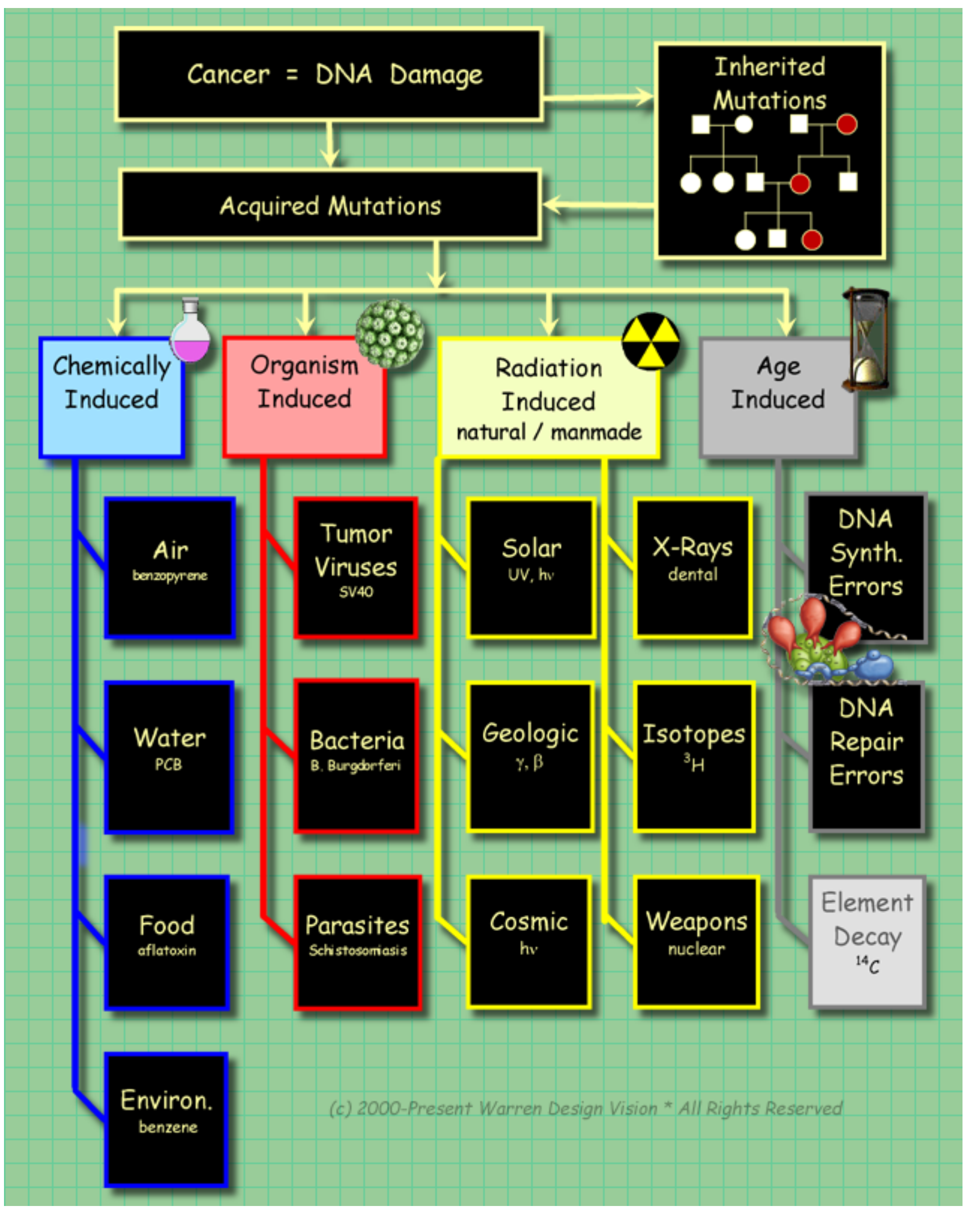


Figure excerpt from - Noise Analysis in Ligand-Binding

In loose terms, the cell is a noisy Turing machine, a complete entity that obtains energy from the outside world and manages information in the nucleus via DNA, RNA, transcription and translation activities [1, 2].

These transcription and translation activities are subject to noise and errors from various sources. For the case of cancer, these noise and error sources are cataloged below:



Four Categories of Mutation

Energetics

The energy component is delivered in the form of glucose, which through the mechanism of oxidative phosphorylation in over 1000 mitochondria per cell is converted into the energy cartridges of ATP and GTP, which are recycled as ADP and GDP to power all the enzymatic reactions within the cell of which there are about 20,000 kinds. And yes, that, like the cell it describes, is a running sentence.

Information Management

Information is not only managed inside the cell through DNA and RNA activities, but also at the surface of the cell through the GPCR receptors. The GPCR receptors are unique chunks of logic, each responding to a specific ligand or agonist in proportion to the degree to which that ligand represents the ideal target of the receptor. The receptor's response can be quantified in terms of the binding affinity for the ligand. Some bindings are irreversible, some are transient.

Modeling as Functions in a Programming Language

We can abstract the operation of any given GPCR as being like that of a function in a programming language. Each GPCR has an input, with a fairly constrained type, and an output corresponding to the activation of the signaling pathway associated with that receptor type.

There are two principal signal transduction pathways involving the G protein-coupled receptors:

- the cAMP signal pathway and
- the phosphatidylinositol signal pathway.

The binding of a ligand to its cognate receptor constitutes a "function call" to the cell. This is a massively parallel process, but despite that, we must still consider each "call" in turn. Then on having elucidated the exact pathway, we need to quantify the amount of parallelism necessary to produce a given degree of response by the cell.

Performance Metrics and Questions

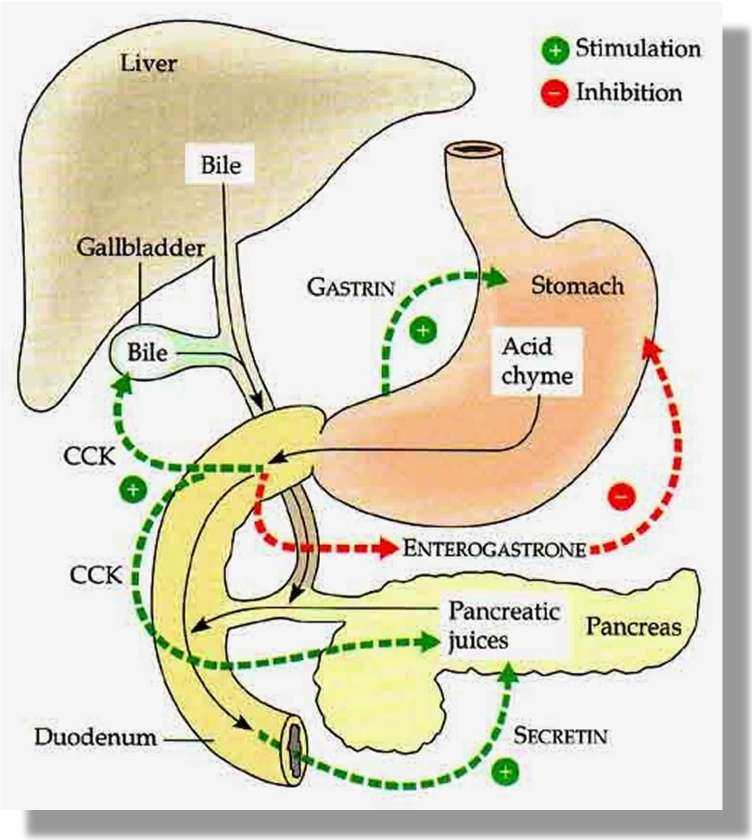
Q1: How many receptor activations are required to get the cell to take a given action? Freeze fracture studies of hormone receptors show dramatic changes in total cellular configuration mere seconds after the cell is exposed to the hormone. Constitutive activation shows that in some case this number is zero.

Q2: How many firings or uses of a given GPCR receptor can take place in its lifetime?

Q3: Is lifetime determined by the ligand environment?

Q4: How is the used GPCR recycled by the proteasome apparatus?

Q5: How many copies of each receptor type appear in the cell walls of each tissue type? We know that the drug tolerance for opioids is related to the number of copies of the receptor currently manifested on the cell wall.

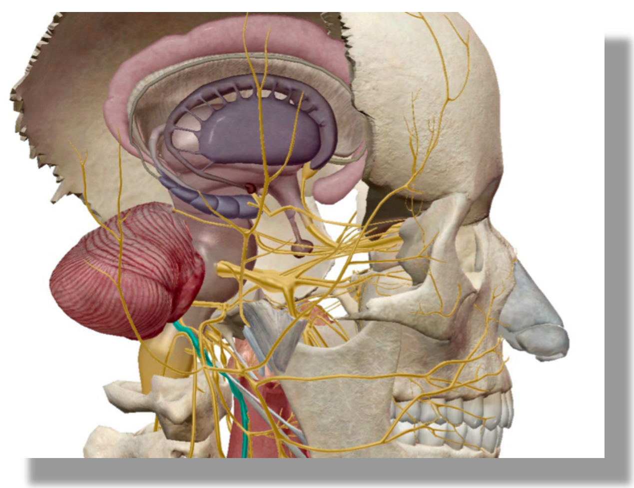


GPCRs in Digestion

Consider the small protein ligand Cholecystokinin (CCK) that has different roles in different organs. Gall bladder cells contract releasing bile when they are exposed to CCK. In the pancreas CCK causes the release of digestive enzymes. The point is that one signal, can produce multiple responses, in multiple organs at different strata of organization. An excellent discussion of this is here.

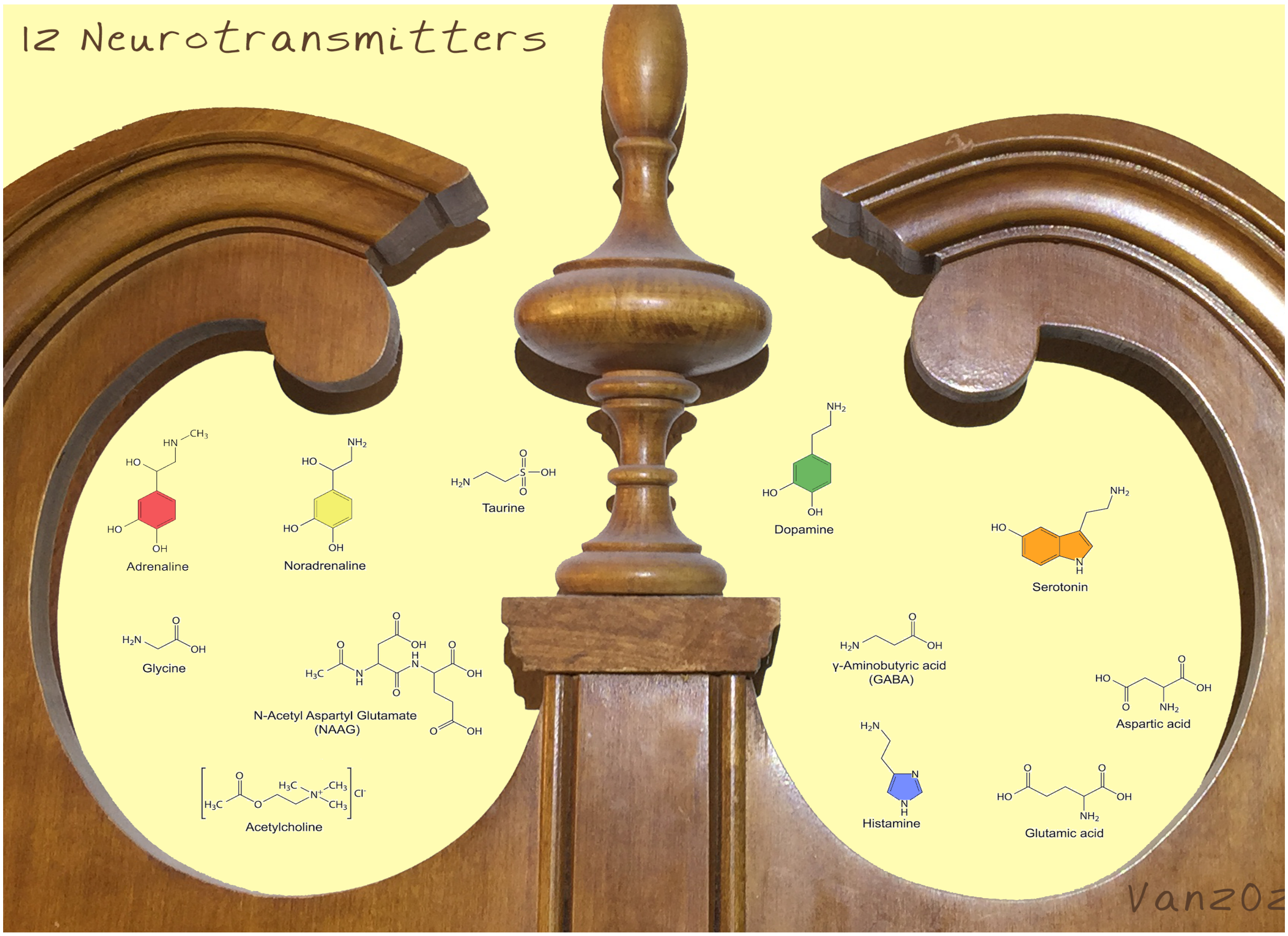
The Scent Genome – Inter Organism Signaling

The extracellular signaling of scent and the large investment that olfactory receptors and scent molecules have in the genome.
According to the Human Genome Project, humans have 400 functional genes coding for olfactory GPCR receptors with 600 additional nonfunctional pseudo genes. Together these comprise 3% of the genes in the human genome. These receptors are members of the class A rhodopsin-like family of GPCRs.



Twelve Neurotransmitters are GPCR Ligands

GPCR's have not only roles between cells in different organs, say as neurotransmitter, hormone and regulatory receptors, but also between completely different organisms, species and kingdoms. The smell of a rose is communication between the person and the plant at great phylogenetic distance! Thus, their importance cannot be overstated. Nerve cells expose their receptors in the intrasynaptic portions of their axons and dendrites as implied by the figure above.



This piece of furniture reminded me of a synapse, so I ran with it. Cats suffer from [Taurine deficiencies](#).

Mathematical Rigor in Abstraction

Mathematical functions emerge having a one to one correspondence between input and output. Functions with multiple inputs still traditionally produce one output. When multiple outputs occur the word, "Relation" is used instead of the stricter "Function". Phrases like "one to one" and "onto" appear in discussions of these. More generally we can talk about:

a. 1 to 1 relations
b. 1 to many relations
c. many to 1 relations
d. many to many relations.

The point is that ligands and their receptors, including GPCR's are in the many to many relation category.

GPCR Ligands as a Broadcast Medium

Claude Shannon placed information theory on a firm mathematical footing in the form of, "A Mathematical Theory of Communication."
We can think of GPCR networks in such terms: GPCR's are like little radio receivers that wait to receive specific signals with some permissible variation. From a communication point of view GPCR activation looks like large bio molecule receivers responding to a small molecule broadcast. When a small molecule like a hormone is broadcast, all cells expressing a receptor for that hormone are eligible to receive and act on that signal. There are many instances of hormone molecules that are engaging many instances of their receptor, in the many to many relationship identified above.

Stationary and Circulating Cells

Somatic cells are locked into a quasi-stationary matrix where they fulfill their role in the organ, while circulating cells in blood and lymph float freely in plasma or lymph corresponding to their roles. Circulating cells are more spheroidal, exposing the entirety of their surface area and receptor population to the fluid in which they are immersed.

Concurrency

The computational point here is that the logic of the cell, as manifest by the GPCR population, as said before has enormous potential for concurrency. A single cell expresses a multitude of GPCR types simultaneously at any given moment and it is interesting to consider just how many different kinds of activities are going on at once in what is a massively parallel processor. It is interesting to consider how this concurrency is managed, say in the instance of conflicting signals. Each GPCR instance can be viewed as its own functional stimulus-response pathway which is reminiscent of Skinnerian Reinforcement Learning.

Inventory

One essential measurement that must be made is to know the inventory of receptors and types that a cell is expressing in each of its operational phases. This measurement must be made for each of the over 200 cell types, whose roles are influenced by the receptor populations they are expressing. This inventory, this "receptor census", must be taken and tabled for both the normal and pathological cases, cataloging normal and exceptional wildtypes in the process. The goal of simulating dynamic processes within the cell is facilitated by the creation and curation of such receptor databases. As mentioned above this inventory is well underway. [1, 2, 3, 4]

Three Segments of GPCR's

GPCR's consist of three key segments:

1) An extracellular domain. This determines the outward facing 'front-office' function of the receptor.
2) A seven alpha-helix transmembrane spanning segment that serves to anchor the receptor in the cell wall, colloquially, much as a sheet rock anchor serves to hold a picture on the wall.
3) An intracellular domain. This folded protein sequence determines the inward facing 'back-office' function of the receptor.

Two Additional Interface Segments

A) The interstitial sequence linking the extracellular domain to the transmembrane spanning segment.
B) A similar sequence that links the transmembrane spanning segment to the intracellular signaling segment.

A Slight Complication

There is a slight complication to including these two additional interface segments which can be seen in the Rhodopsin diagram above. The linking sequence consists of a **separate** sequence for each of the seven transmembrane alpha helix for segments A) and B) described above for a total of fourteen. For this reason, it may prove simpler to characterize GPCR's as consisting of three key segments. When rigor compels us to inspect these interface segments, they can be numbered Interfaces[1-7] on the extracellular side A) and the intracellular side B. For brevity this might look like Interface4Inside, or Interface3Outside or some other suitable notation.

Synthesis and Deployment

GPCR's are typically synthesized and topologically expressed as the involution of a bubble impinging from the inner cell surface and 'popping' to express the extracellular segment to the outside world, while simultaneously becoming itself a part of the cell wall and expressing the intracellular segment to the signaling apparatus inside the cell. Arrestins are proteins that interact on the cytosolic side to block the signaling of the GPCR.

The Maddening Case of Dimerization

Some GPCR's work in pairs and even in groups, wherein it is necessary for an external ligand to force a dimerization of two neighboring receptors bobbing like fishing floats in the cell wall, before the intracellular signal is transmitted.

Categories of Function and Malfunction

The three segments of GPCRs can:

a) Function as intended, with some characteristic binding affinities and ligand binding and exchange rates. Recall that at these scales most extracellular reactions are facilitated by the high-speed wiggling, the fine Brownian motion, that allows receptor and ligand to come within proximity to each other to enable orientation and binding to occur. These processes can be characterized by mathematical binding constants that reflect the structure of both receptor and ligand, along with the conditions of the media in which the binding is taking place.

b) Function, but in a degraded capacity. In this situation the binding constants are outside some normal distribution of expected value but are adequate for some degree of cellular function.
c) Non-functional, but non-pathological. In this case the receptors are synthesized and expressed, but cause no harm to the cell, and are supplemented by other receptors that function as in cases a) or b) above, possibly using a non-silenced sequence from another locus on the genome, using one contributed by the other parent. The receptor synthesis itself may take a correct RNA sequence, but fail to transcribe the sequence directly, as in the case of the BRACA1 transcription factor. BRACA1 is the famous gene from breast-cancer whose mutation can affect the quality of copies being made by the copying machine so to speak.
d) Non-functional and pathological. In this case the receptors are synthesized and expressed but cause harm to the cell and host, by activating signaling pathways that are undesirable. A classic example of this is hormone receptors that spontaneously dimerize or fire a growth signal without the dimerization of the ligand providing the instruction do so. Her2Nu being a classic example of this problem.

Error Rates

Now these are the things that COULD happen, the question before us is to characterize the frequency with which they DO happen and to recognize the mechanism of existing therapies that exploit these and propose and construct new therapies which also exploit them.

Hardware and Software Abstractions

To drive this abstraction thing home, a slight deviation is in order. In 1958, Jack Kilby at Texas Instruments came upon a key idea that complex electronic circuits could be printed, instead of soldered together. This small, and in retrospect, possibly obvious idea, gave rise to the computer revolution as we know it today. The key ingredient of the idea was that the circuit that defined the operation of the integrated circuit, or IC, could be analyzed, replicated and manufactured using a two-dimensional projection of what is in reality a three-dimensional device. When I was talking about, "The Abstraction" above, I was borrowing from the Kilby playbook noticing that the architecture, functioning, analysis, and drug-design for GPCR's could follow a similar pattern of progress if we could flatten out each GPCR, view its sequence, and treat it in effect as a logic circuit, with the three components enumerated above.

Realism vs. Representation: Flattening

1) Flattening enables direct observation of the three components of each GPCR and comparison of the sequence with variants, normal and pathological.
2) Separating concerns teaches us that folding issues can be managed separate as packaging issues are with integrated circuit construction. They are two dimensional devices deployed into a three-dimensional world, and the 2D nature is just a formalism that enables us to divine into layers what we want the IC to do.

3) Flattening enables us to create symbols, that like typography enable us to make rapid detection of both function and anomaly. The eyes are sensitive to detail and miss none of it on close scrutiny.
4) Amplifying this point. The three domains of GPCRs are symbols, in some divine lexicon if you will. This lexicon is something that we can learn to read and understand. It is a language in which the logic of the cell in its relation to the outside world is defined. It is a language in which simulations and communications are facilitated. Humans are, if nothing else, linguistically capable creatures. Mapping the liquid squishy, mucoid world of the cell to concrete communications is a very desirable way to proceed. And in that way, I must apologize that my Abstraction is really just a Concretion! It gives us a basis for designing tools that enable the understanding, and when indicated, the modification of these life-giving chunks of logic.
5) Flattening distorts the 3-dimensional reality of a ligand settling into the pocket of the extracellular GPCR domain in a profound way but simplifies the indexing and cataloging of function.

Comparative Anatomy of GPCRs

Now that we have defined and flattened the three segments of GPCRs we can do a comparative anatomy of them. We can catalog what they do. We can measure or calculate their characteristic or activity constants. We can group them by function in a Linnaean kind of activity. We could make a periodic table of GPCR's, something manageable best by computers, themselves built of defined and flattened things. Making a periodic table is a bit artificial of course, since the attribute upon which we sort GPCRs is different than valences and atomic number. There is an analogy however, in that even isotopes of elements can be viewed as mutant variants of the most frequently occurring wild-types!

Two Lessons from History

Before the advent of clinical laboratory technology, before the contributions of chemistry and physics there were village priests and medicine men. The afflictions of diabetes had been documented on papyrus by Hesy-Ra since 1552 BC, but diagnosis was inaccurate, and the ravages of the disease were profound – from comas in the young to loss of eyesight and limbs in the aged.

The Need for Visualization

In these historic times there were two major clues, obtained through the senses, and running no less on the G-Protein Coupled Receptors of this paper. The first clue was that flies would gather around urine that contained sugar. A second clue was a sweet and heavy breath, whose scent was reminiscent of a drunken person. Instead of being drunk the diabetic was literally exhaling ketones that had accumulated in an alternate metabolic route for excess sugar. This sugar, unable to be processed by the insulin gatekeeper rose in concentration in the blood, where when exposed to the capillary endothelium, the cells of the retina, and the nerves was toxic and over time caused degeneration resulting in amputations, blindness and peripheral neuropathy.

The Town Drunk, the Taste of Urine

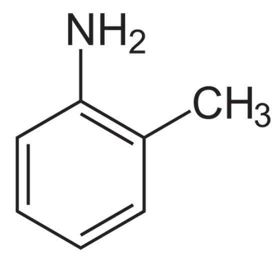
When sugar levels in the unfortunate diabetic climbed sufficiently high, behavior was affected in a way that resembled drunkenness. People were sometimes imprisoned for this drunken behavior, and in the worst case, lapsed into a ketoacidotic coma and died. Thomas Willis in 1674 advocated tasting urine to detect the excretion of excess sugar. French physician Apollonaire Bouchardat noted that glucose disappeared from the urine of some diabetics as a result of war-related food rationing. Italian diabetes specialist Catoni counseled those afflicted to reduce their sugar and bread intake. Two parallel revolutions would converge to replace these unseemly circumstances with the bright light of measurement.

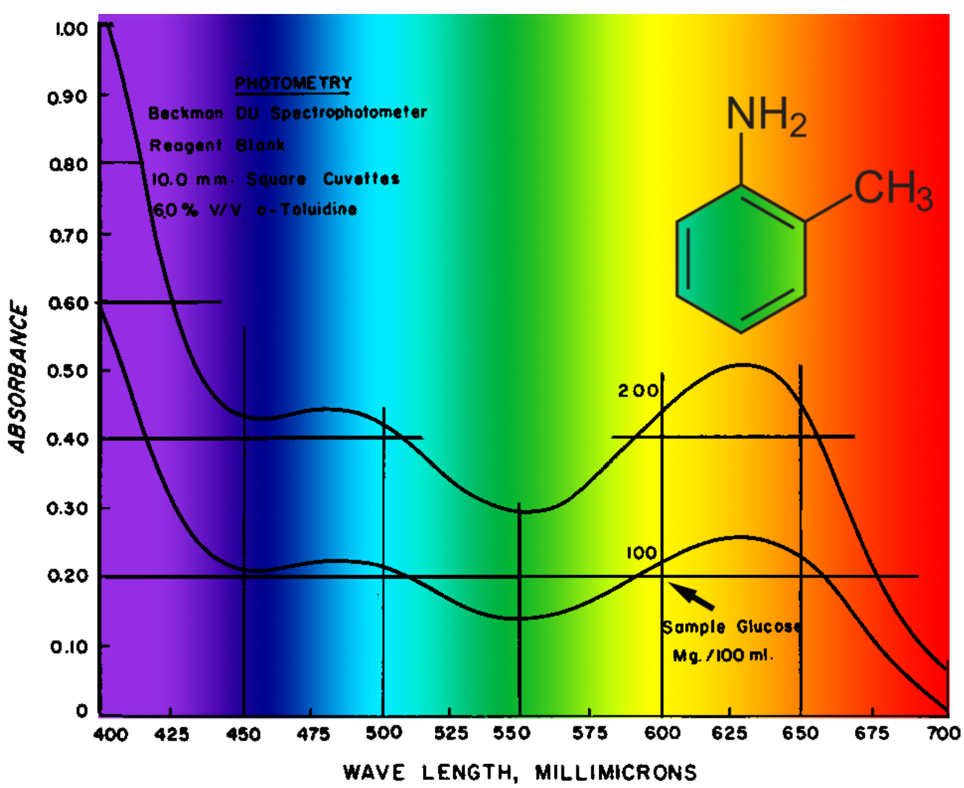
Spectroscopy and Beer's Law

One revolution was that of spectroscopy in physics and chemistry and the construction of instruments, that through Beers law of absorbance, could measure the concentration of a chemical species in an optical cuvette, a special test tube that was engineered for the transmission of light.

A second revolution, consisting of three separate advances enabled a visualization process, which ultimately led to direct measurement. The three advances were:

- the sterile drawing of blood
- the centrifugation of said blood which separated it into plasma, a white cell buffy coat, a column of red cells
- The mixing of the plasma with ortho-toluidine and acetic acid, produced a green color by absorption of the reds at 630 nm whose intensity was directly proportional to the blood glucose of the patient.





Absorption spectra of *o*-toluidine reaction with glucose.

Visual inspection of the colorimetric changes were qualitatively accurate. Spectroscopic measures of those changes were quantitatively accurate enabling precise tracking of blood glucose over time, saving many lives.

It was the **visualization** of the glucose concentration that led to the revolution in the treatment of diabetes. This same process would also revolutionize the measurement of many other blood-borne remnants of metabolism.

Maps Count

"Every cell is a world, and every world needs an atlas."

It is nice to have a list of cities that we might want to visit and understand. It is nice that associated with each city are important statistics like its population, its budgets, its assets, its goods and its services.

But to get around in the world, we need more than a directory of cities, we need a map that shows the geographic and geometric relationships of those cities to each other. A map that can tell us the order in which we might want to visit those cities. Navigation is enabled by maps. Maps enable discovery.

Traveling Salesman Problem

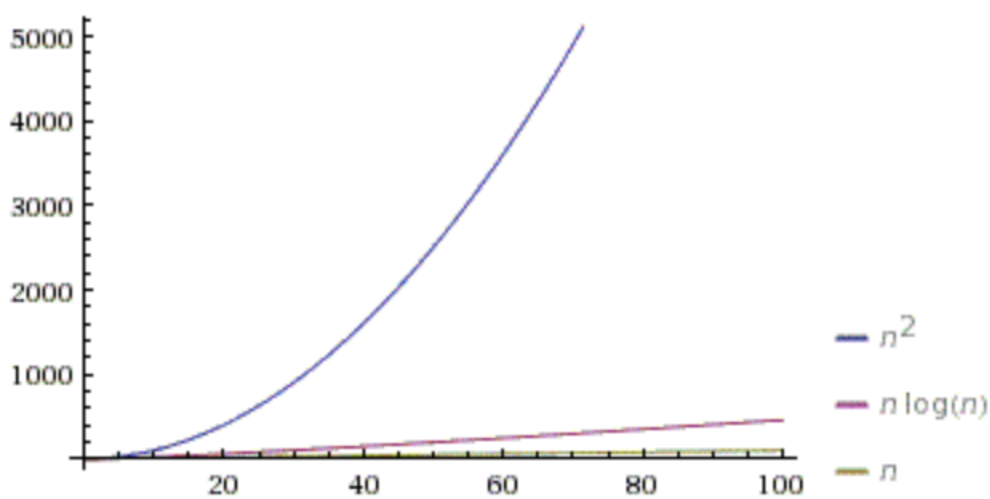
There is a famous problem in computer science called, "The Traveling Salesman Problem", or TSP for short. TSP, which remains uncomputable for more than a few cities to this day, describes, given a list of cities and their locations, the best order in which to visit them to minimum driving distance. Nature has addressed the problem of sequential visitation with willy-nilly broadcasting to get its message across.

Even phone companies need maps and switching systems. These have emerged to make sure that we use less copper than silicon in connecting every person on earth to, potentially, every other person on earth.

Connectivity

Forgetting for a moment our wireless present:

If we had to have one wire to connect every person to every other person on Earth, as in the pre-wireless day, there just wouldn't be enough copper to connect them. This is because connecting 8 billion people to 8 billion other people requires 8 billion squared connections – 64 billion if you're counting. But it is possible to exploit the fact that not all 8 billion people are talking to all 8 billion other people at the same time, so intermediate switching nodes can handle the traffic by routing it through switches, which brings us to our present-day wireless situation.



*n*n vs n * log(n) connectivity driving copper vs. silicon in communication networks*

I bring up the need for an atlas and the switching problem in nearly the same breath for the following reason.

Ubiquity of Communication

G-Protein Coupled Receptors are the nodes in a chemical, hormonal, and pheromonal communication network that regulates all aspects of cellular life. GPCRs allow cells to communication between themselves, to other cells in the same organ, to other cells in other organs, and to other cells in other instances of organisms including people, plants and insects.

ReceptorWorld™

The hope is, that creating a table of cellular logic, much like an engineering handbook of integrated circuits, would be a useful tool in bioinformatics. To that end, a prototype of this process was begun September 2003 by the author creating something called ReceptorWorld™ which is here.

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54964 Sep  2  2003 AcetylcholineReceptorType4a.gif
21827 Sep  2  2003 AdenosineReceptorA2b.gif
31437 Sep  2  2003 Adreno-Release-CorticotropicHormoneReceptor.gif
54591 Sep  2  2003 AlphaAdrenalinReceptorType1b.gif
32752 Sep  2  2003 AlphaAdrenalinReceptorType2b.gif
54690 Sep  2  2003 AnaphylatoxinReceptorA.gif
39247 Sep  2  2003 AngiotensinType2.gif
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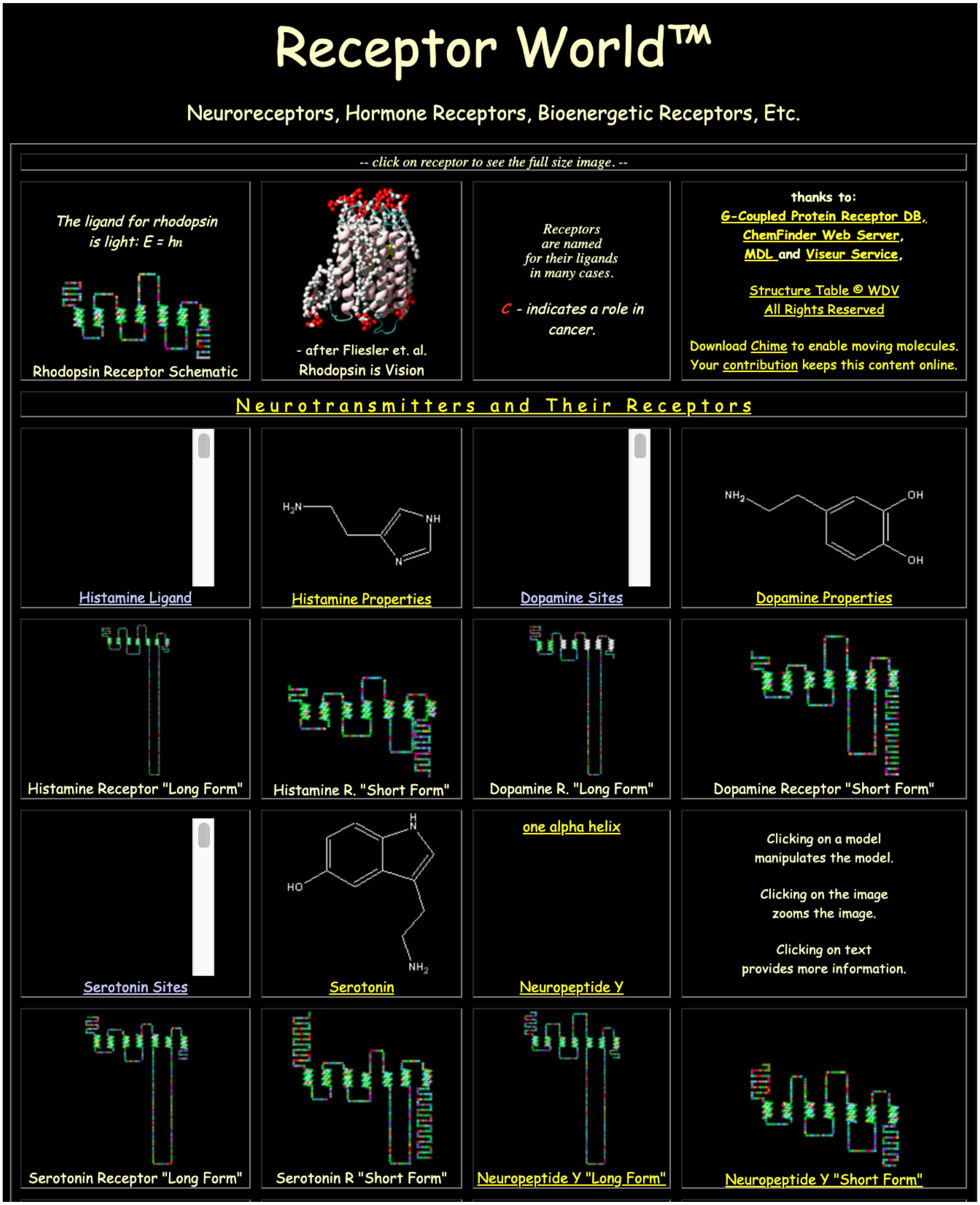
It has languished somewhat, being superseded by other more excellent and well-funded efforts. One area of evolution has changing chemical representations from MDL Chime format, championed by pioneer Eric Martz to current formats like JMOL and JSMOL used on Wikipedia. A very useful effort that jumped started this work was the program [] by [] to for doing comparative anatomy of GPCR's. This has morphed into gpcrdb.org a great resource for the analysis and comparisons proposed here.

Stepping past these vagaries of history; The Protein Data Bank contains data and visualizations tables for many known human GPCRs, some with ligands in play. [1, 2, 3, 4] This services is similar to the Online Mendelian Inheritance in Man (OMIM) site, maintained by the National Institutes of Health.



Receptor World by the author