ORIGINAL RESEARCH PAPER

A Spectroscopic Mechanism for Primary Olfactory Reception

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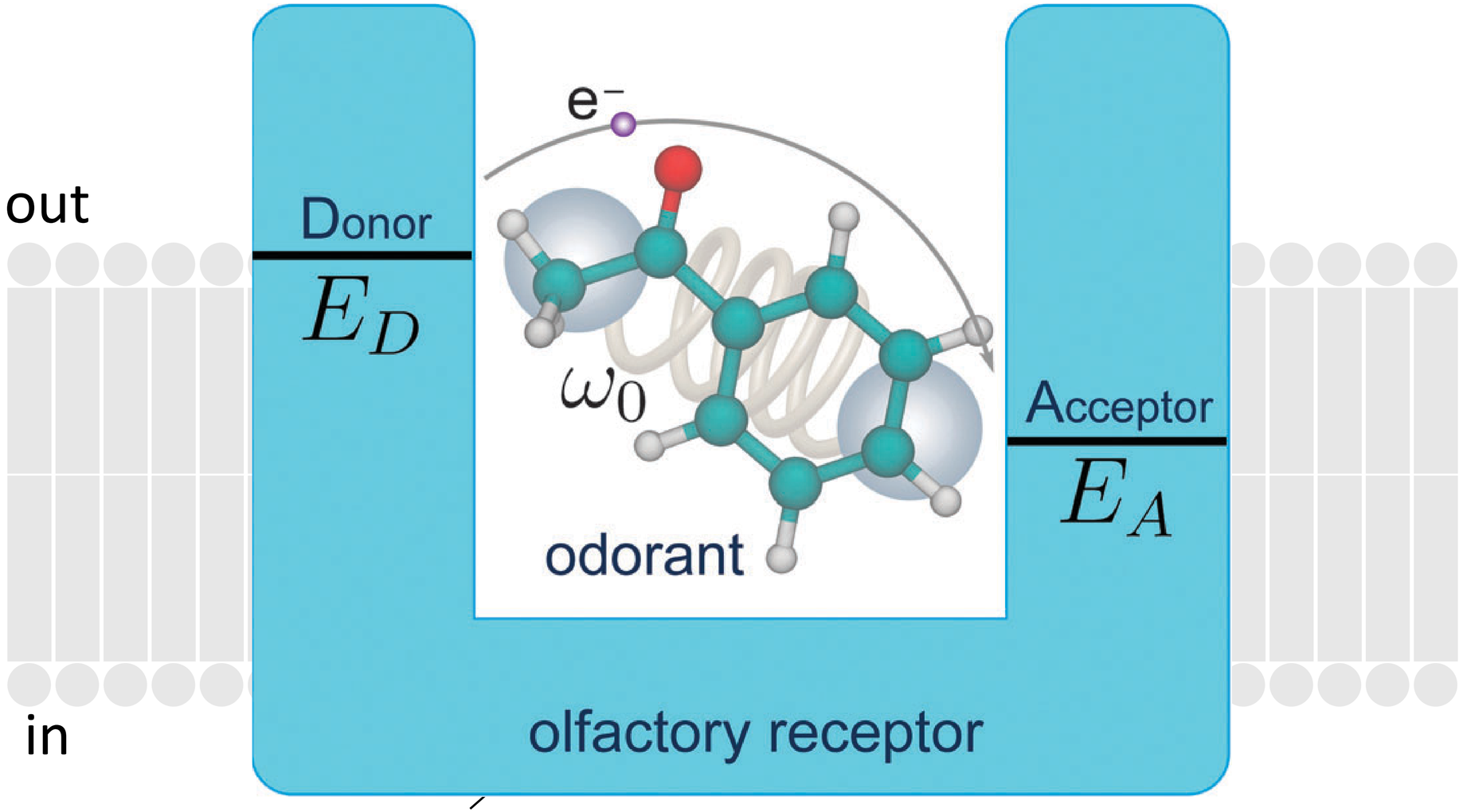
Abstract

A novel theory of primary olfactory reception is described. It proposes that olfactory receptors respond not to the shape of the molecules but to their vibrations. It differs from previous vibrational theories (Dyson, Wright) in providing a detailed and plausible mechanism for biological transduction of molecular vibrations: inelastic electron tunnelling. Elements of the tunnelling spectroscope are identified in putative olfactory receptors and their associated G-protein. Means of calculating electron tunnelling spectra of odorant molecules are described. Several examples are given of correlations between tunnelling spectrum and odour in structurally unrelated molecules. As predicted, molecules of very similar shape but differing in vibrations smell different. The most striking instance is that of pure acetophenone and its fully deuterated analogue acetophenone-d_8, which smell different despite being identical in

vertebrate olfactory receptor



Could Humans Recognize Odor by Phonon Assisted Tunneling?

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(Received 10 July 2006; published 16 January 2007)

Our sense of smell relies on sensitive, selective atomic-scale processes that occur when a scent molecule meets specific receptors in the nose. The physical mechanisms of detection are unclear: odorant shape and size are important, but experiment shows them insufficient. One novel proposal suggests receptors are actuated by inelastic electron tunneling from a donor to an acceptor mediated by the odorant, and provides critical discrimination. We test the physical viability of this mechanism using a simple but general model. With parameter values appropriate for biomolecular systems, we find the proposal consistent both with the underlying physics and with observed features of smell. This mechanism suggests a distinct paradigm for selective molecular interactions at receptors (the swipe card model): recognition and actuation involve size and shape, but also exploit other processes.

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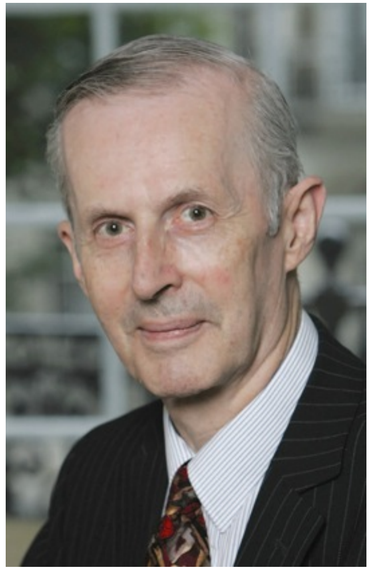

Molecular vibration-sensing component in *Drosophila melanogaster* olfaction

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Edited by Obaid Siddiqi, National Center for Biological Sciences, Bangalore, India, and approved January 14, 2011 (received for review August 19, 2010)

A common explanation of molecular recognition by the olfactory system posits that receptors recognize the structure or shape of the odorant molecule. We performed a rigorous test of shape recognition by replacing hydrogen with deuterium in odorants and asking whether *Drosophila melanogaster* can distinguish these identically shaped isotopes. We report that flies not only differentiate between isotopic odorants, but can be conditioned to selectively avoid the common or the deuterated isotope. Furthermore, flies trained to discriminate against the normal or deuterated isotopes of a compound, selectively avoid the corresponding isotope of a different odorant. Finally, flies trained to avoid a deuterated compound exhibit selective aversion to an unrelated molecule with a vibrational mode in the energy range of the carbon–deuterium stretch. These findings are inconsistent with a shape-only model for smell, and instead support the existence of a molecular vibration-sensing component to olfactory reception.

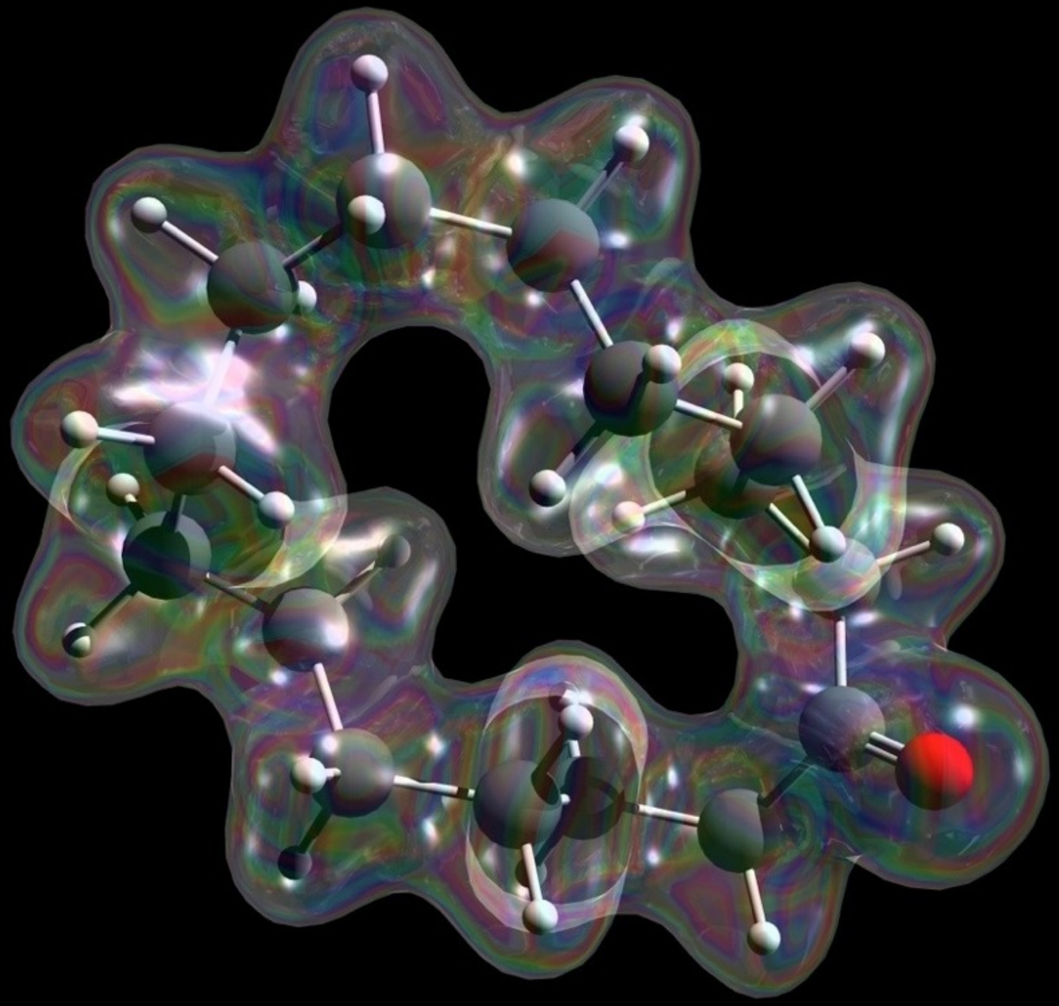
Olfactory systems perform remarkable feats of molecular recognition, but although much is known about the neurophysiology of olfaction (1–5), how olfactory receptors "read" molecular structure remains unknown. Parts of odorant molecules (odotopes) have been proposed to engage particular receptors in a "lock-and-key" manner and this molecular shape recognition mechanism is thought sufficient for odor discrimination (2). An alternative hypothesis (6) posits that molecular vibrations of all atoms, or of particular functional groups of odorant molecules, contribute to odor recognition, and odorants with similar vibrational spectra should elicit similar olfactory responses (7). Molecules in which deuterium replaces nonex-

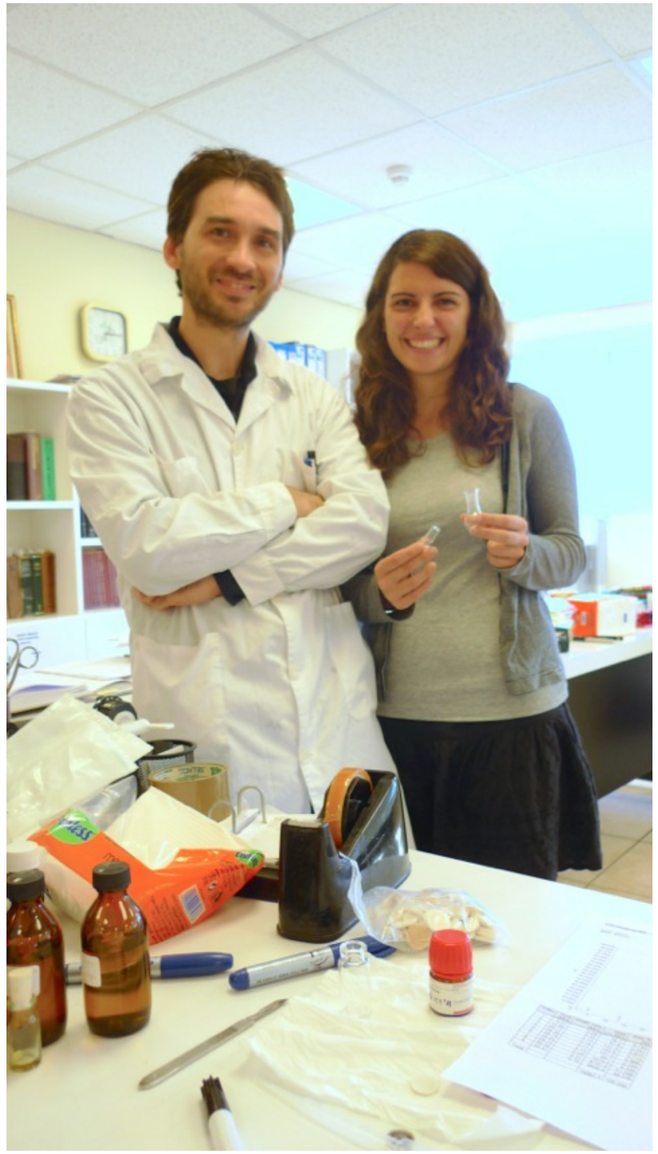
odor character could be distinct and identifiable, irrespective of the structure and chemical properties of the odorant molecules that carry it. Significantly, we used *Drosophila* as unbiased and objective subjects to address this issue. They possess a relatively well understood olfactory system (10–13), exhibit keen olfactory discrimination (14–16), and can be conditioned to selectively avoid or seek odors with the use of established methodology (17, 18). We ask whether *Drosophila* can detect deuterium as a distinguishing molecular feature in odorant isotopes and a salient cue for conditioning. The results of these experiments provide support for the notion that flies can smell molecular vibrations.

Results

Spontaneous Differential Responses to Deuterated Odorants. Although deuteration does not appreciably change molecular shape, atom size, or bond length or stiffness, it doubles hydrogen mass, thus affecting the overall vibrational modes of an odorant. Therefore, if recognition of molecular shape alone was the sole determinant for odor character (2, 3), then flies should not respond differentially to deuterated [d, where $d_{(x)}$ denotes replacement of *x* nonexchangeable hydrogens with deuterium atoms] and nondeuterated/normal (i.e., H-) odorants. To address this hypothesis, we took advantage of the commercial availability of acetophenone (ACP) carrying three, five, or eight deuterium atoms (d_3, d_5, and d_8) in place of the respective hydrogens in the normal molecule (h-ACP). Equal amounts (75 μL) of each odorant were diluted to 1 mL in isopropyl myristate and we quantified (Fig. 1*A*) the response of groups of flies to
5 each odorant versus unscented air traversing the arms of a standard T-maze (*Materials and Methods*) (19, 20). When given

cyclopentadecanone [Exaltone ®]





Dimitris Georganakis & Klio Maniati

Simon Gane & Ian Smith

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Molecular Vibration-Sensing Component in Human Olfaction

Simon Gane[1☯], Dimitris Georganakis[2☯], Klio Maniati[3☯], Manolis Vamvakias[2], Nikitas Ragoussis[2], Efthimios M. C. Skoulakis[3], Luca Turin[3]*

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Abstract

Whether olfaction recognizes odorants by their shape, their molecular vibrations, or both remains an open and controversial question. A convenient way to address it is to test for odor character differences between deuterated and undeuterated odorant isotopomers, since these have identical ground-state conformations but different vibrational modes. In a previous paper (Franco et al. (2011) Proc Natl Acad Sci USA 108:9, 3797-802) we showed that fruit flies can recognize the presence of deuterium in odorants by a vibrational mechanism. Here we address the question of whether humans too can distinguish deuterated and undeuterated odorants. A previous report (Keller and Vosshall (2004) Nat Neurosci 7:4, 337-8) indicated that naive subjects are incapable of distinguishing acetophenone and d-8 acetophenone. Here we confirm and extend those results to trained subjects and gas-chromatography [GC]-pure odorants. However, we also show that subjects easily distinguish deuterated and undeuterated musk odorants purified to GC-pure standard. These results are consistent with a vibrational component in human olfaction.

Citation: Gane S, Georganakis D, Maniati K, Vamvakias M, Ragoussis N, et al. (2013) Molecular Vibration-Sensing Component in Human Olfaction. PLoS ONE 8(1): e55780. doi:10.1371/journal.pone.0055780

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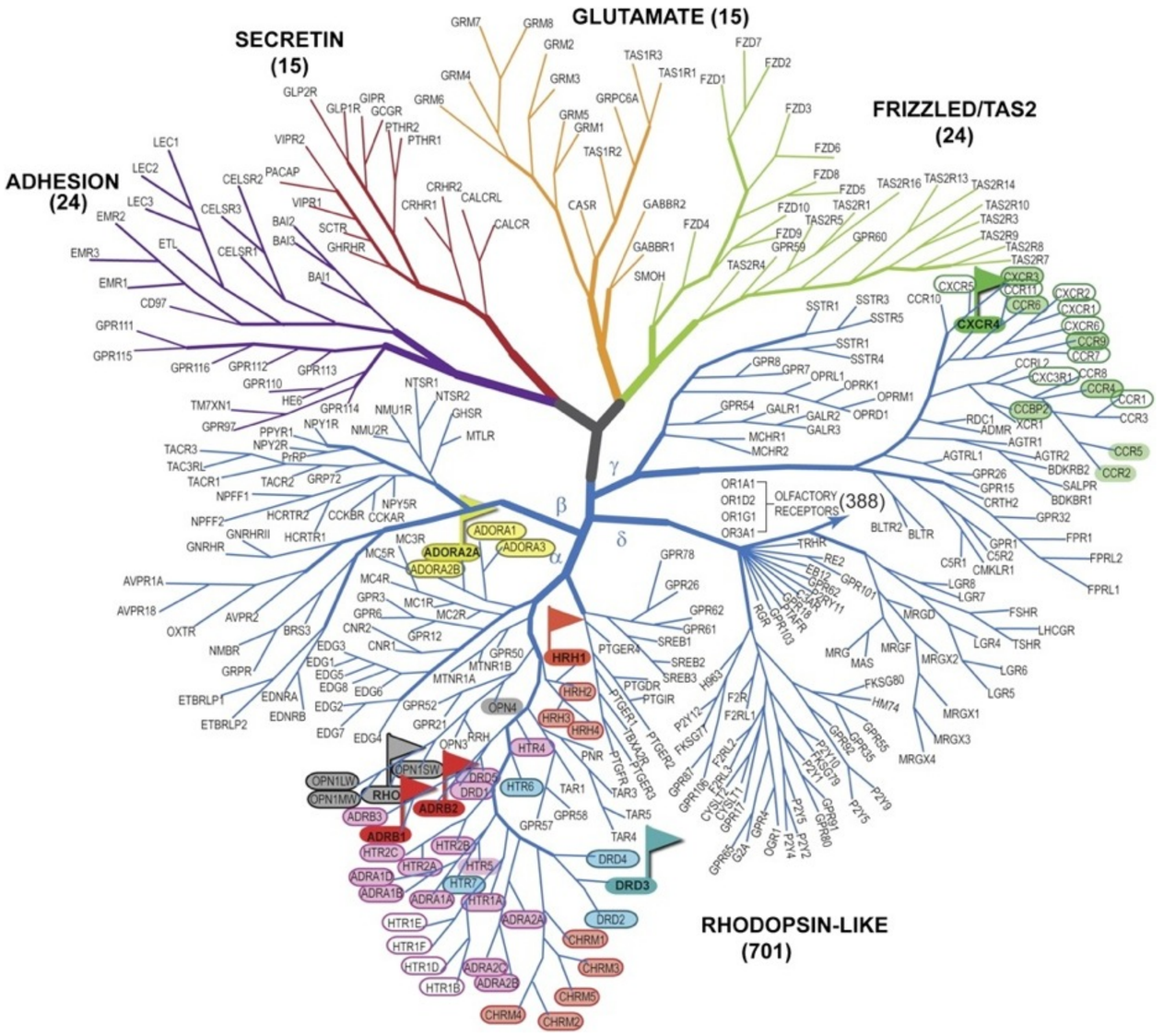
☯ These authors contributed equally to this work.

G-protein receptor phylogenetic tree

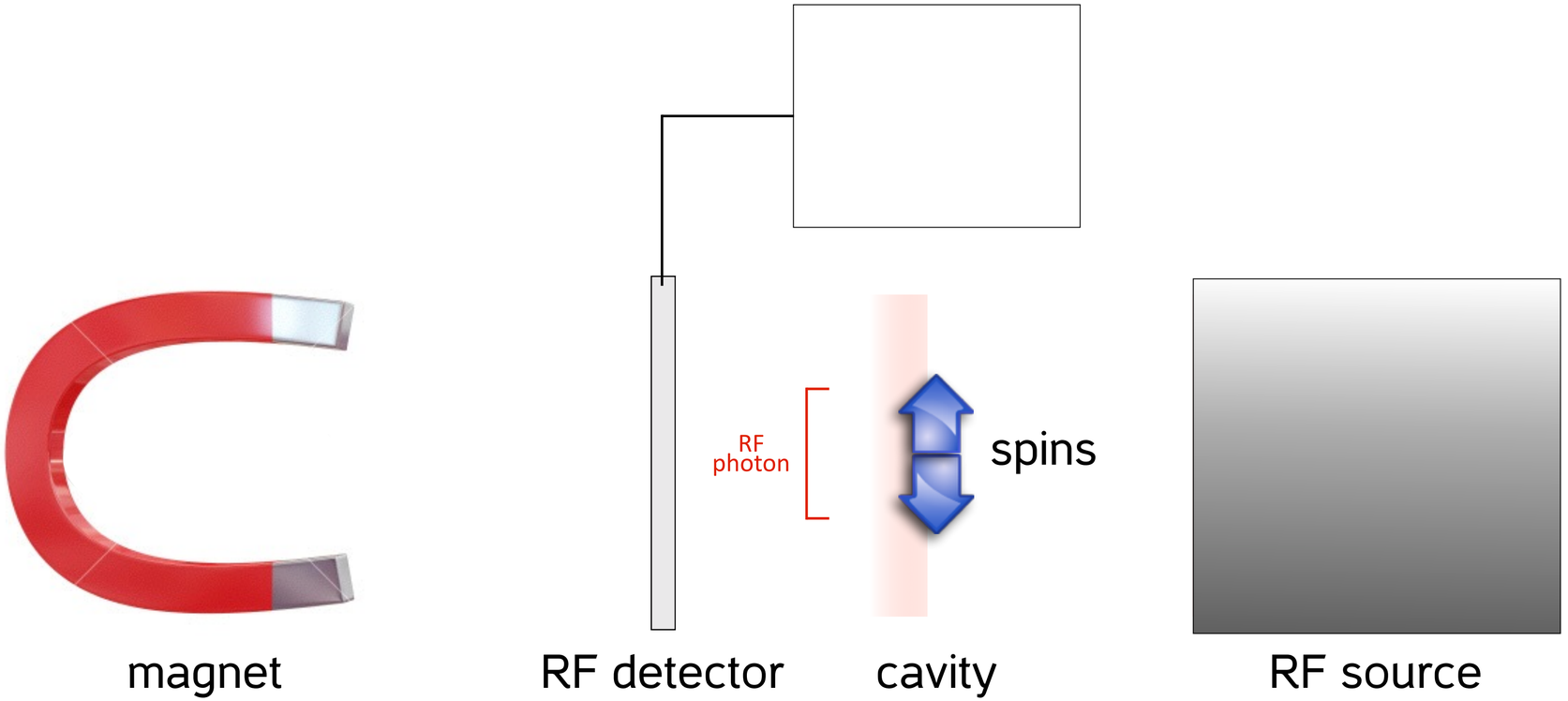


From Kufareva et al. Structure, Volume 19, Issue 8, 10 August 2011, Pages 1108–1126

so maybe

so maybe

how ESR works



electrons in olfaction

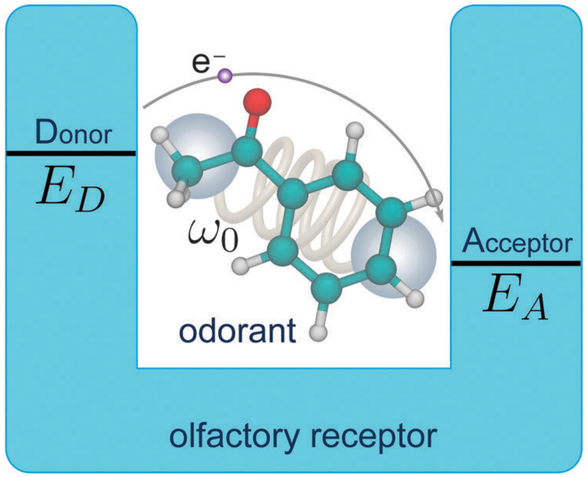
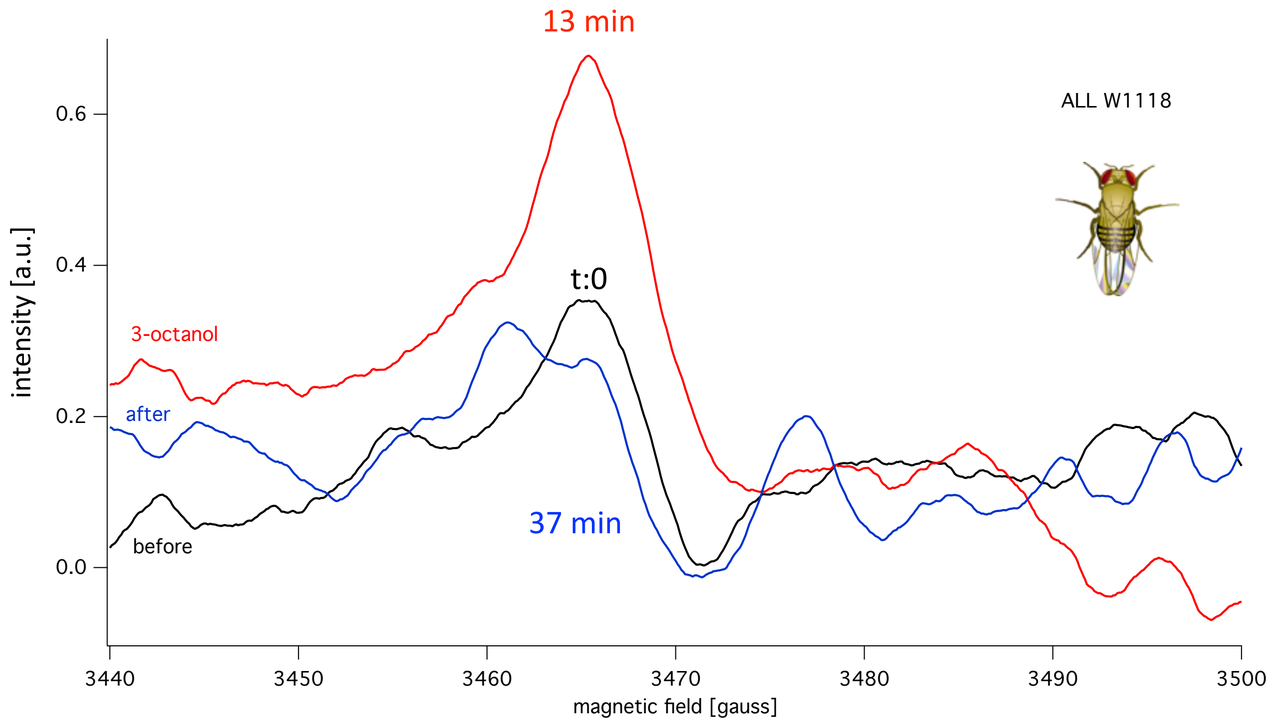


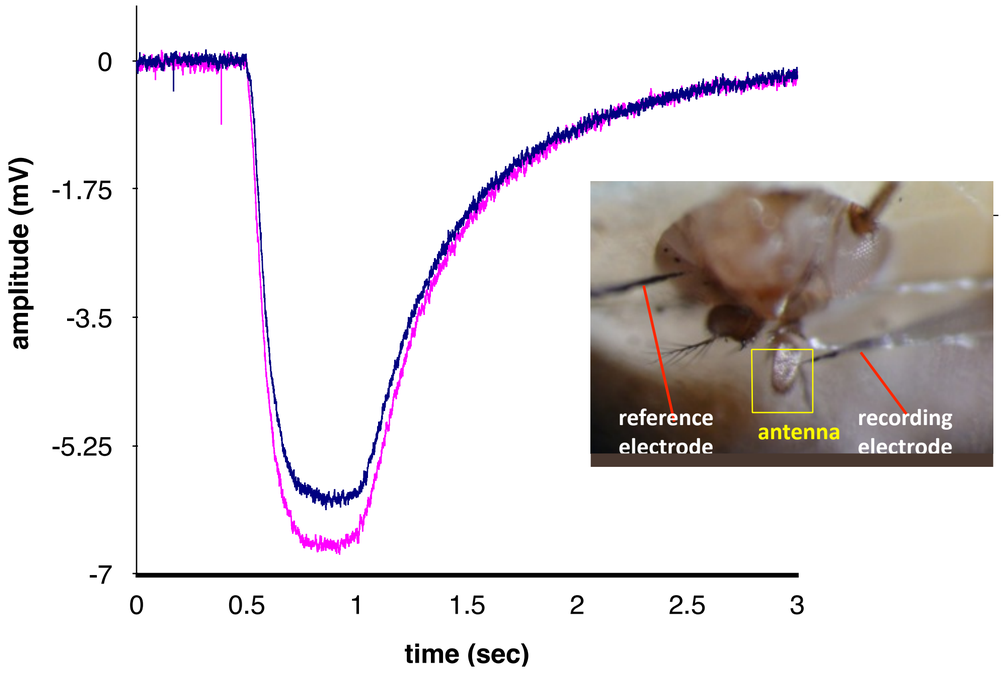
Fig. 1 Principle of vibrationally assisted olfaction. The odorant molecule with characteristic frequency ω_0 binds to the olfactory receptor binding pocket forming an electron–donor–acceptor complex with donor energy E_{D} and acceptor energy E_{A}. Electron tunneling from the donor site to the acceptor site of the olfactory receptor is enhanced if the vibrational frequency of the odorant molecule matches the energy difference $\Delta\varepsilon = E_{\mathrm{D}} - E_{\mathrm{A}}$.

effect of octanol on spin signal of Drosophila



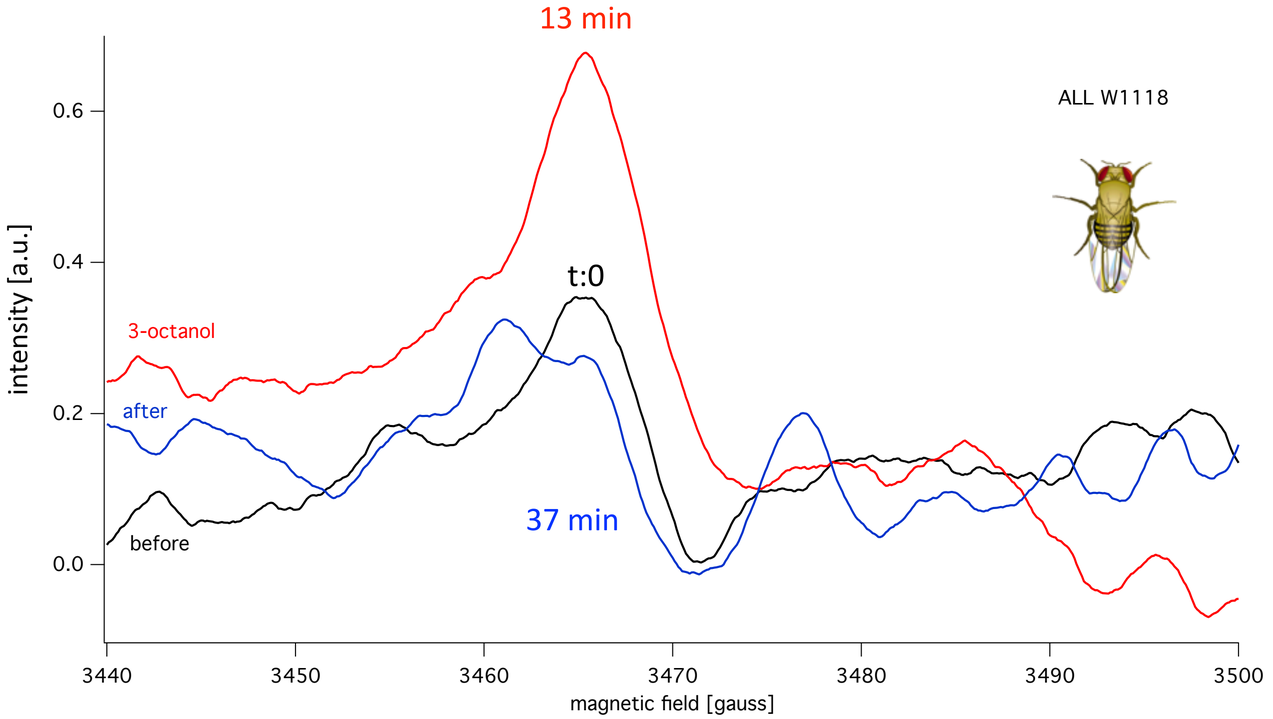
wrong time scale

Drosophila Electroantennagram



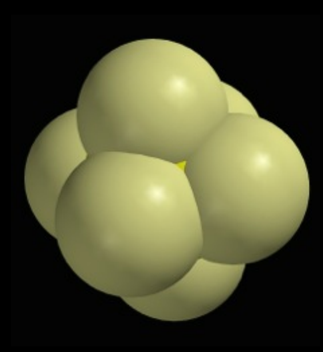
Courtesy of Alexandros Gaitanidis, BSRC Alexander Fleming

effect of odorant on spin signal of Drosophila

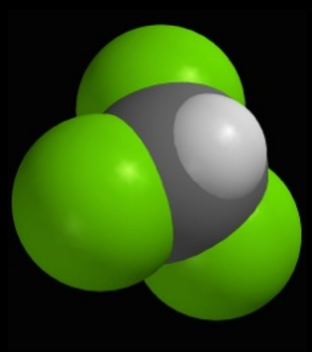


some general anesthetics

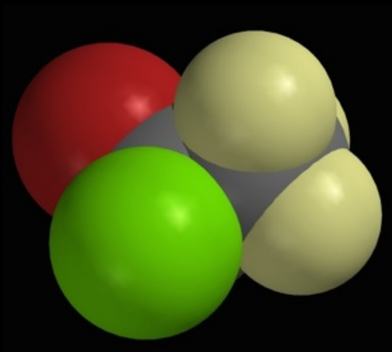
Xe



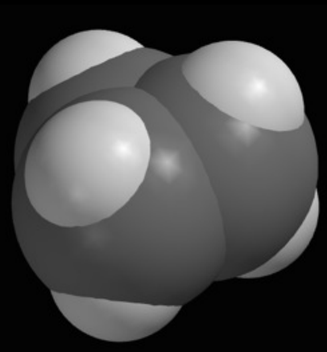
SF_6



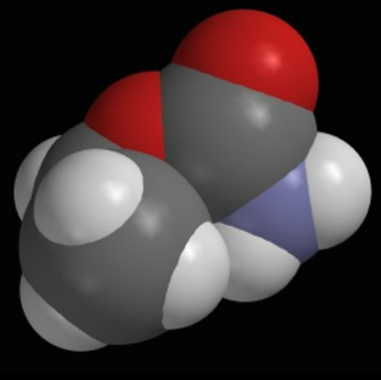
$CHCl_3$



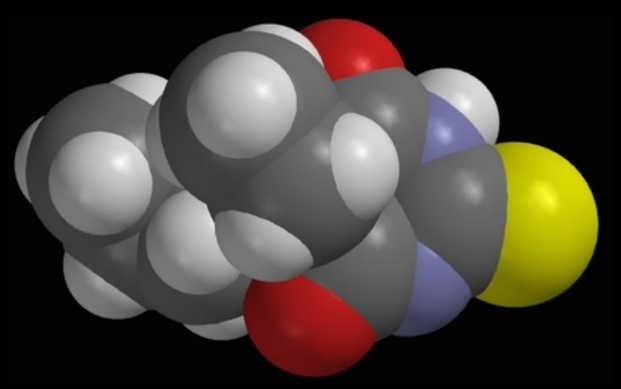
halothane



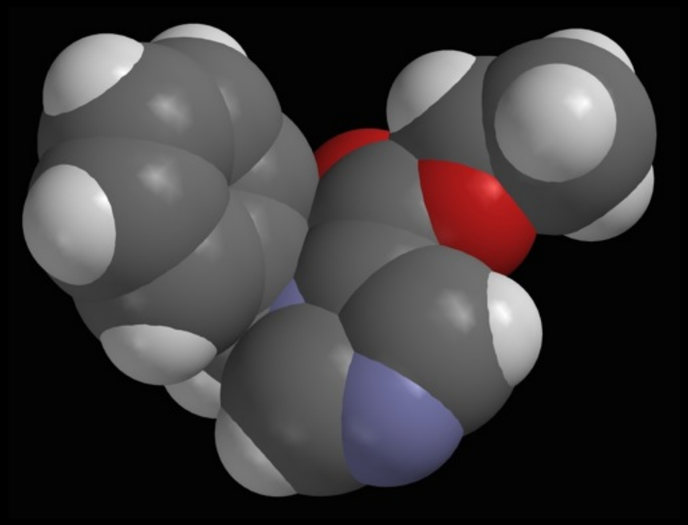
cyclopropane



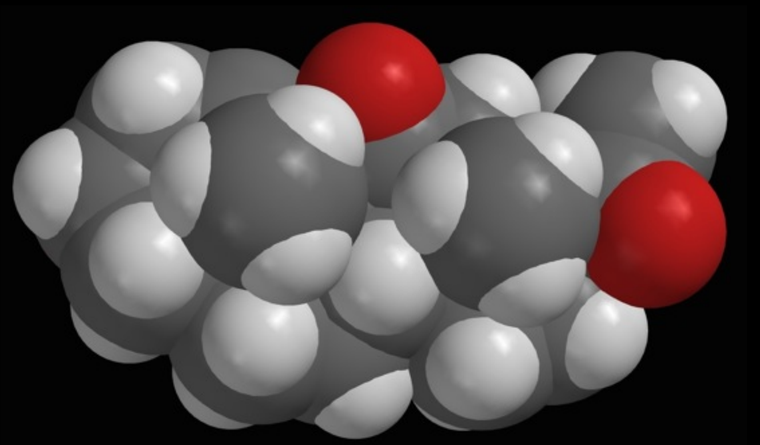
urethane



thiopental

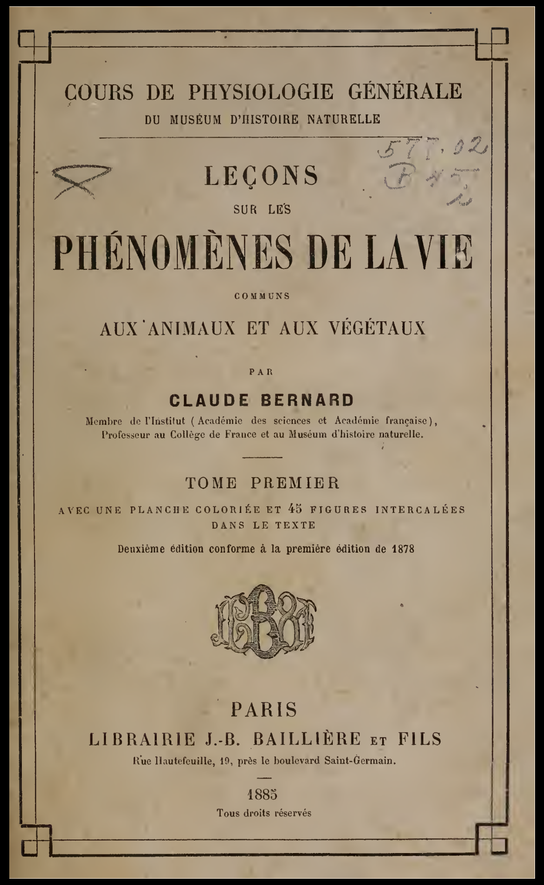


etomidate



alfaxalone

how general are they ?



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AUX ANIMAUX ET AUX VÉGÉTAUX

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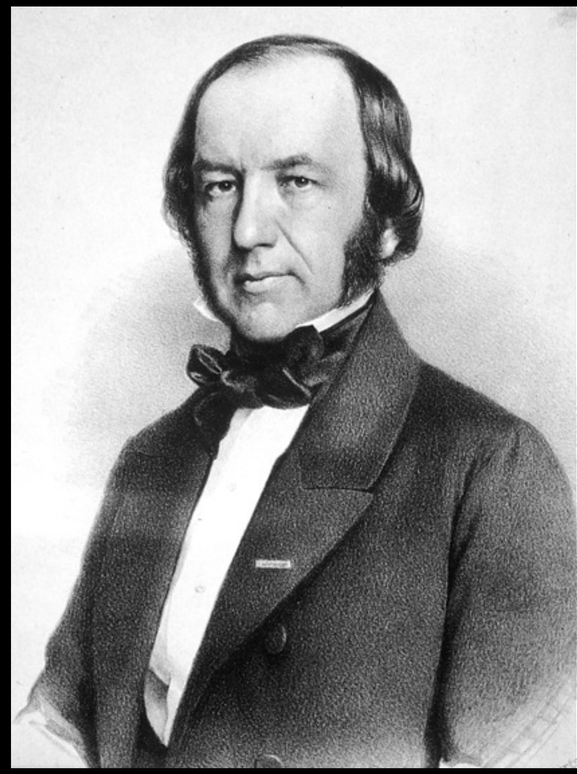
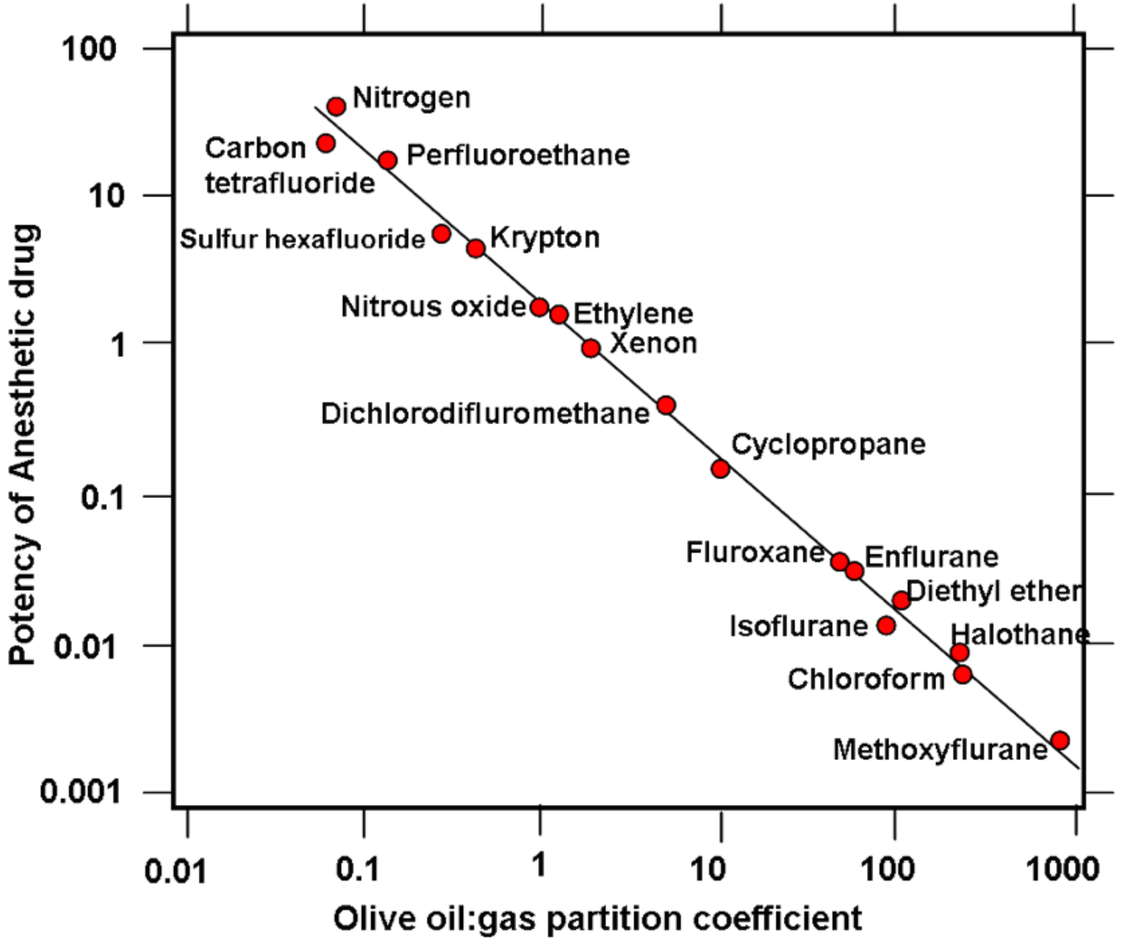
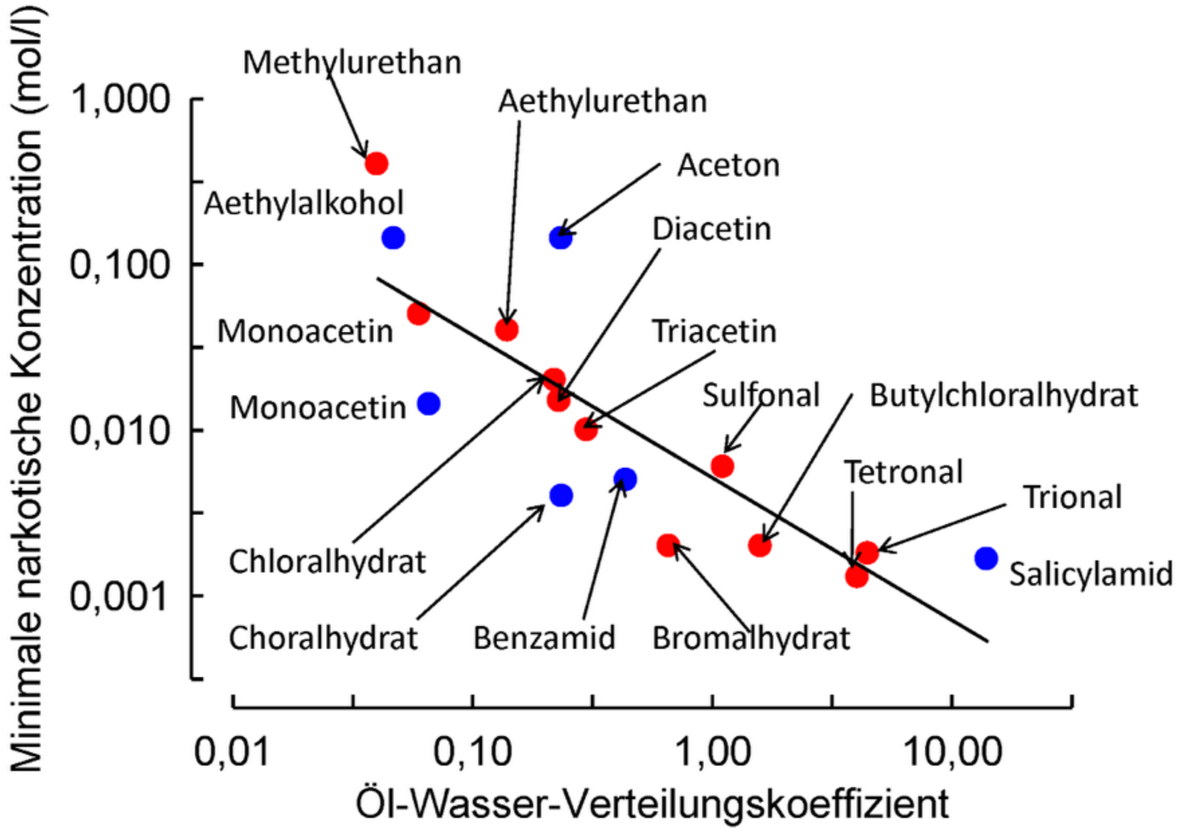


Claude Bernard 1813-1878

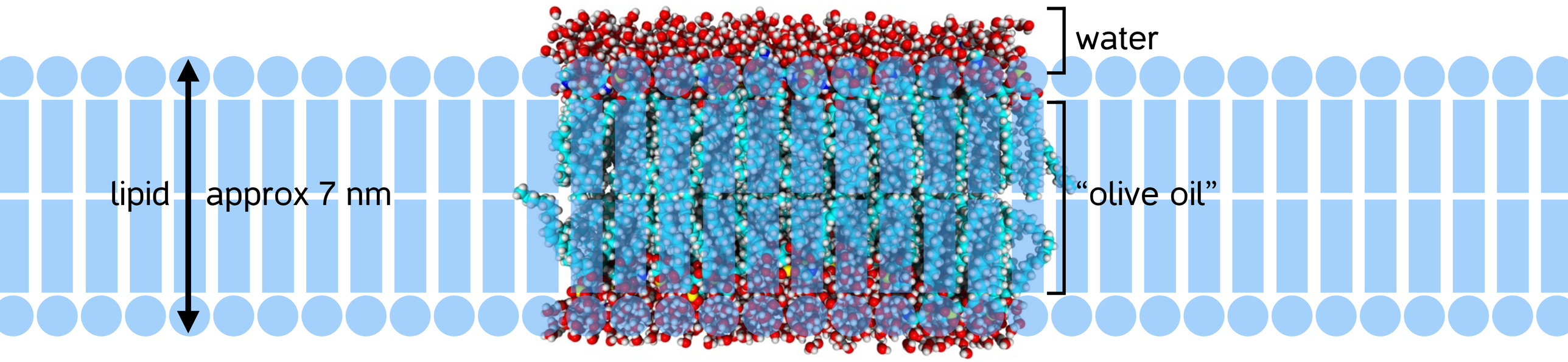
the Meyer-Overton relationship





the cell membrane

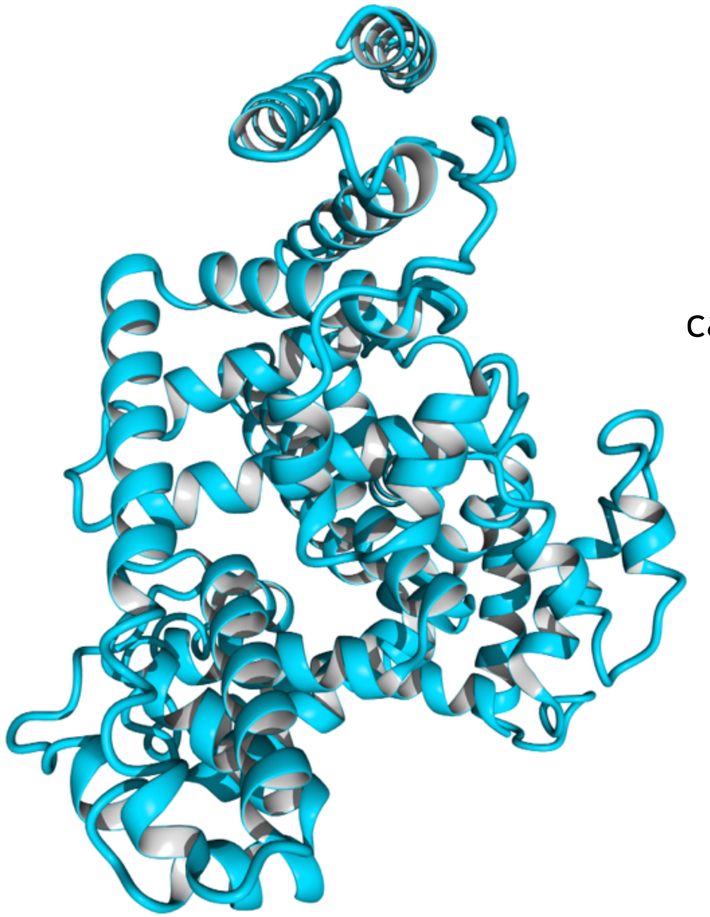
extracellular
water



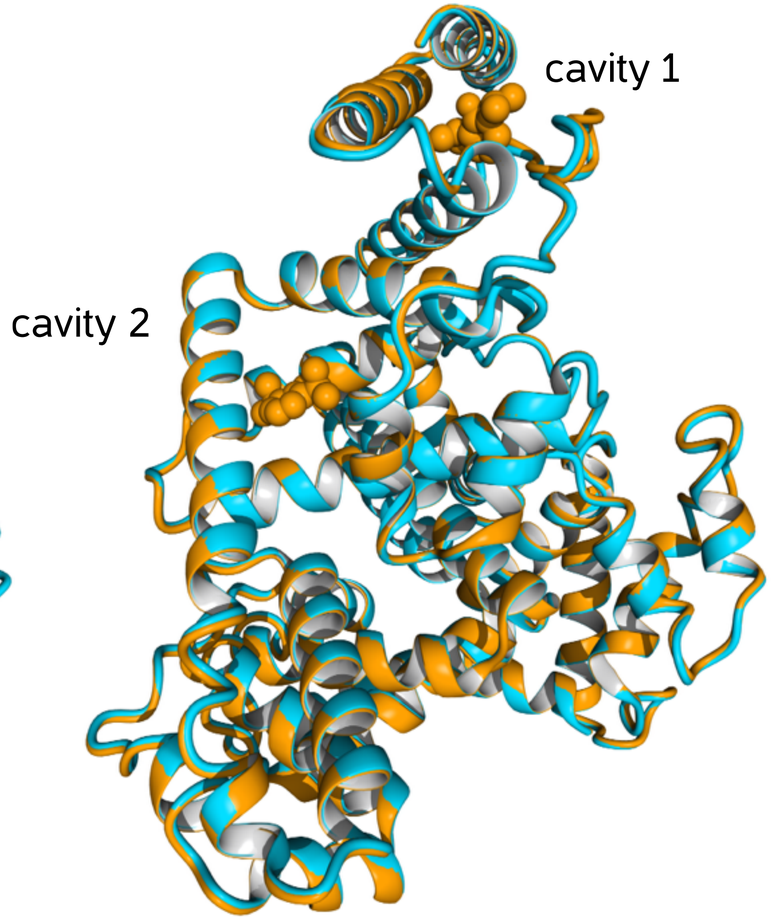
intracellular
water

pdb of bilayer courtesy of Peter Tieleman’s
Biocomputing Group, U Calgary

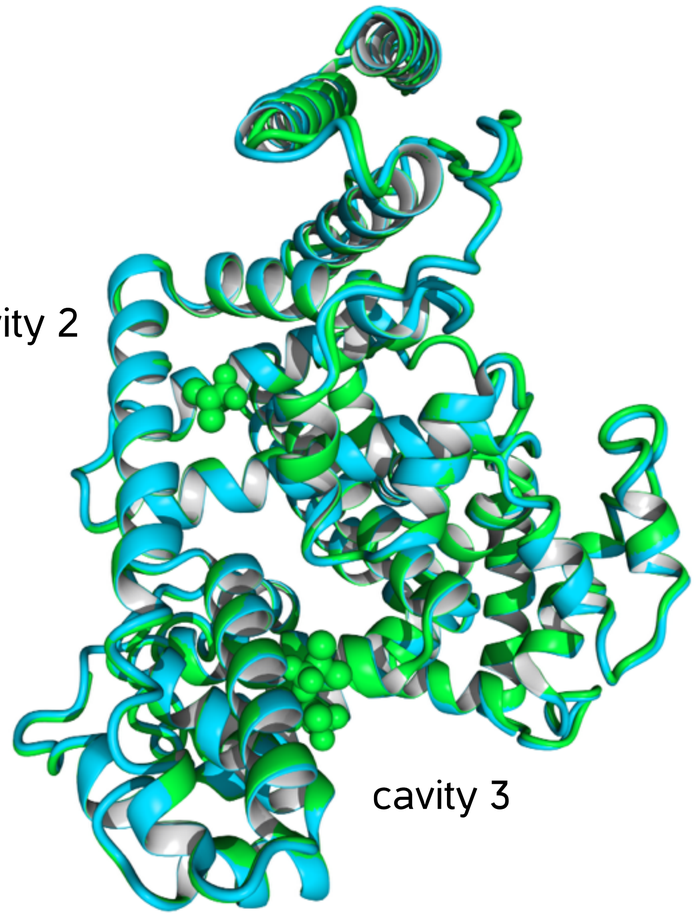
or maybe proteins ?



human serum albumin



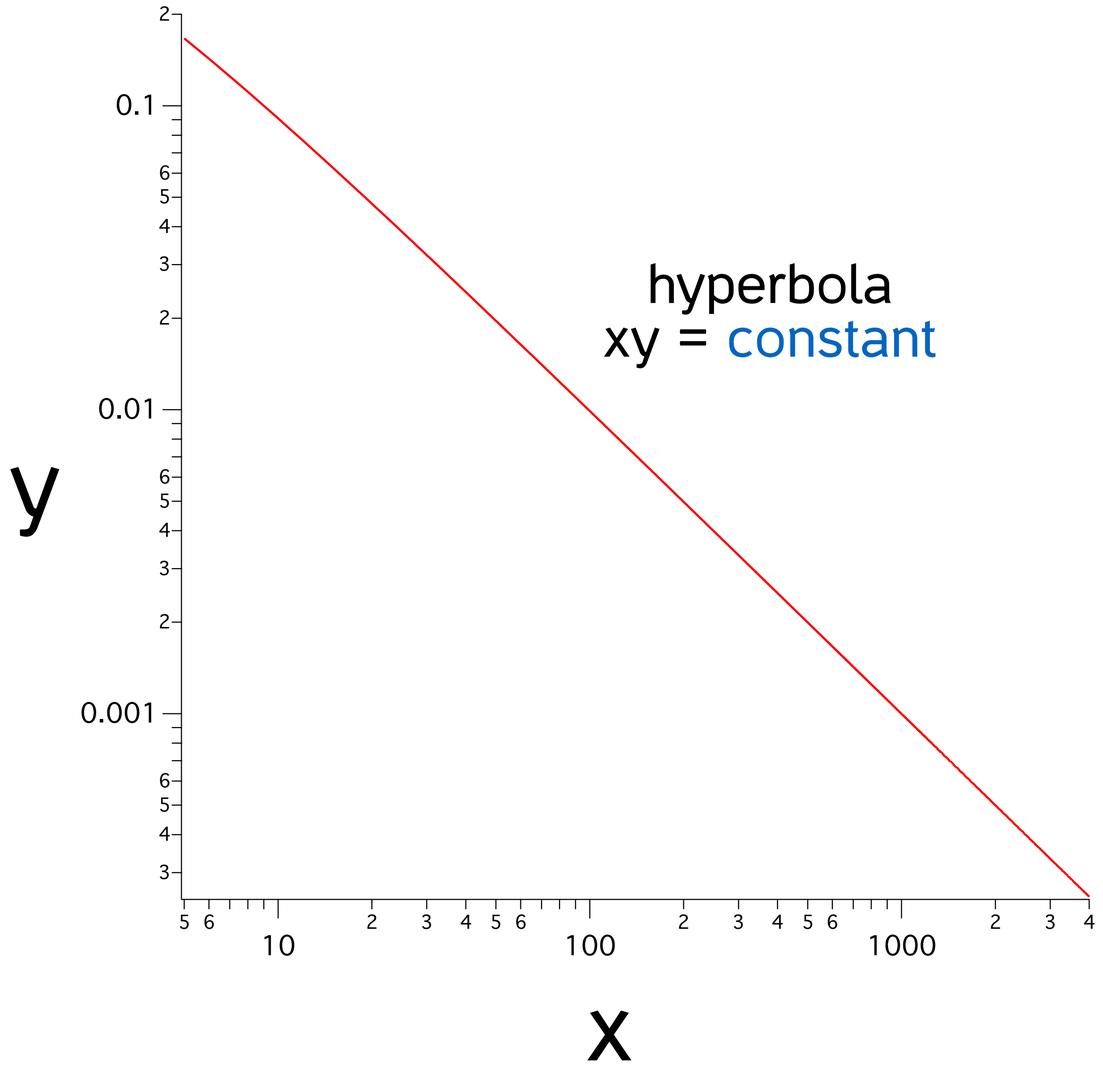
+ propofol



+ halothane

PDB IDs: 1E78, 1E7A, 1E7B
From Bhattacharya et al. (2000) J.Biol.Chem. 275: 38731

what the Meyer-Overton graph means



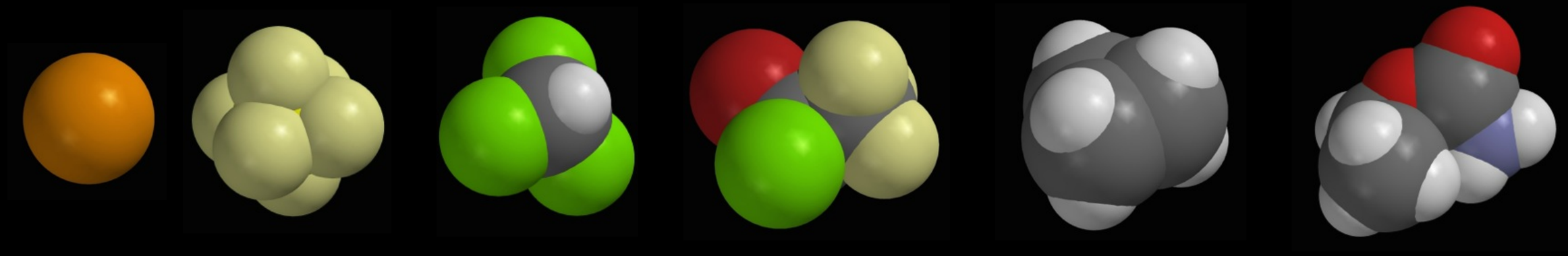
hyperbola
xy = constant

the concentration of anesthetic at the active site[s] sufficient for narcosis is constant regardless of the anesthetic

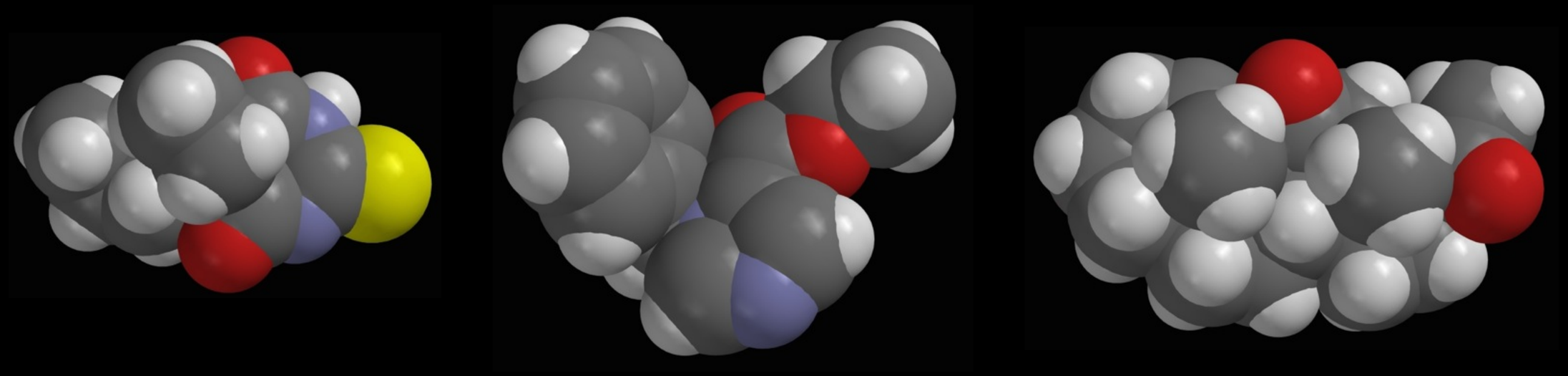
↓

all anesthetics are equally potent

how is that possible ?

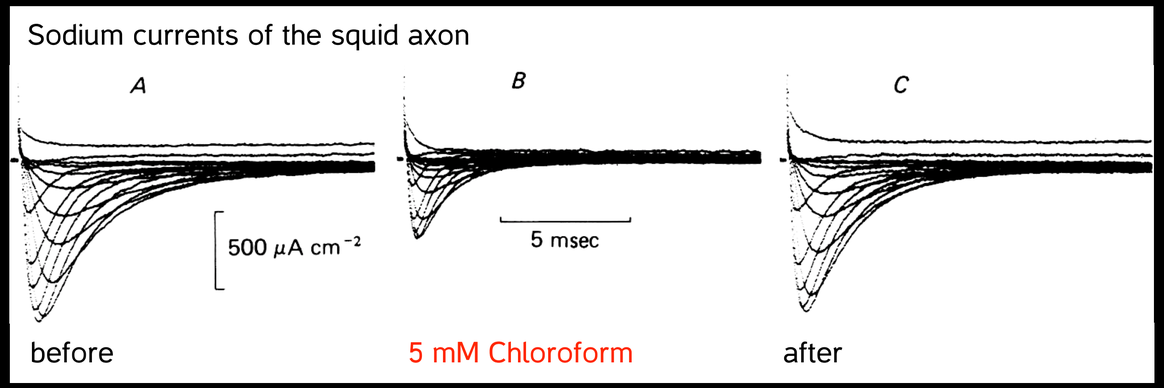


Xe SF_6 $CHCl_3$ halothane cyclopropane urethane



thiopental etomidate alfaxalone

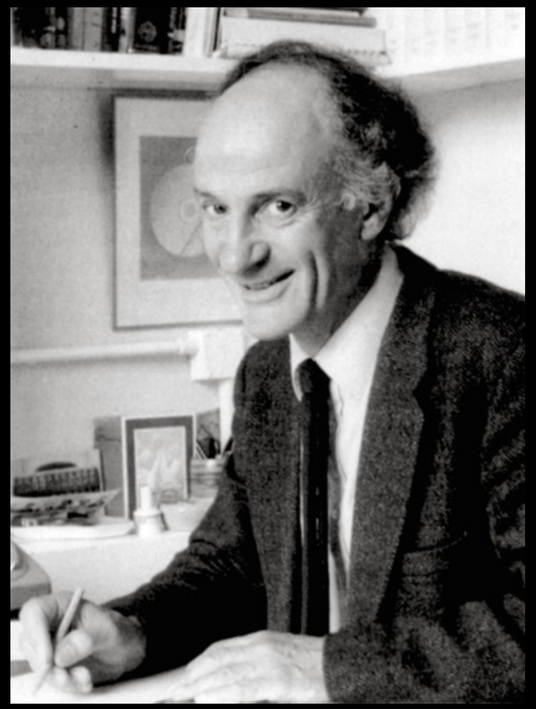
theories of anesthesia: ion channels



J. Physiol. (1983), 341, pp. 429-439

> .5M in membrane !

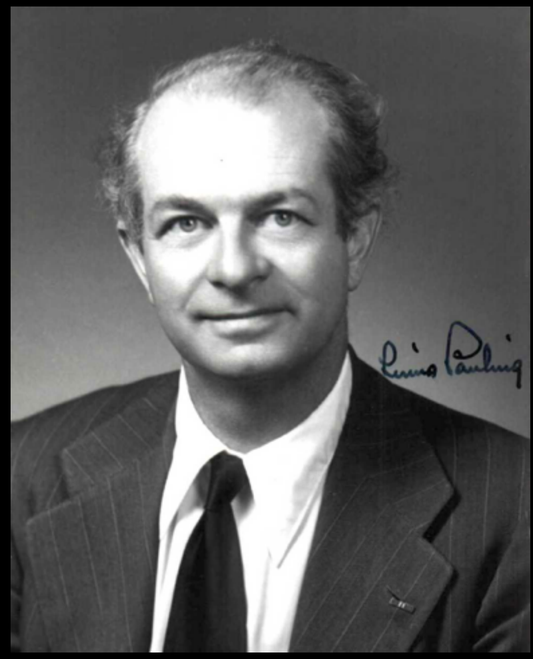
ion channel block



Denis Haydon 1930-1988

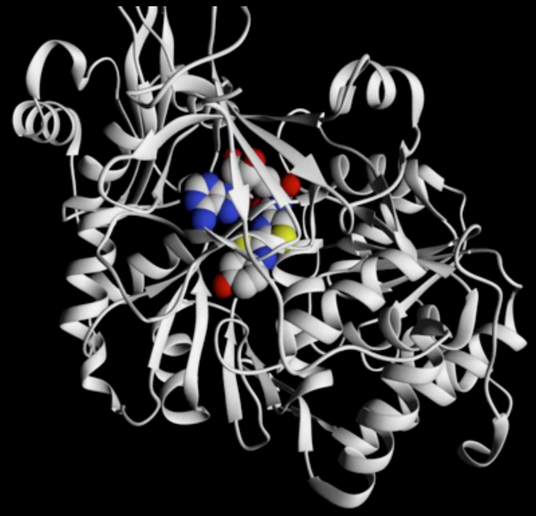
theories of anesthesia: gas hydrates

methane hydrate



Linus Pauling 1901-1994

theories of anesthesia: enzyme inhibition

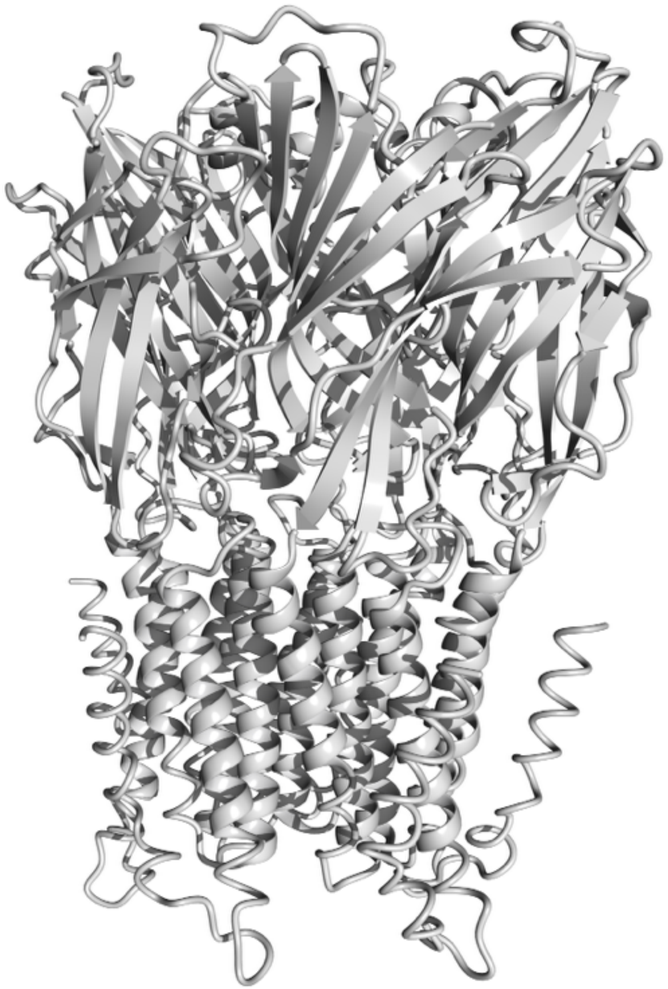


Credit: University of Rhode Island

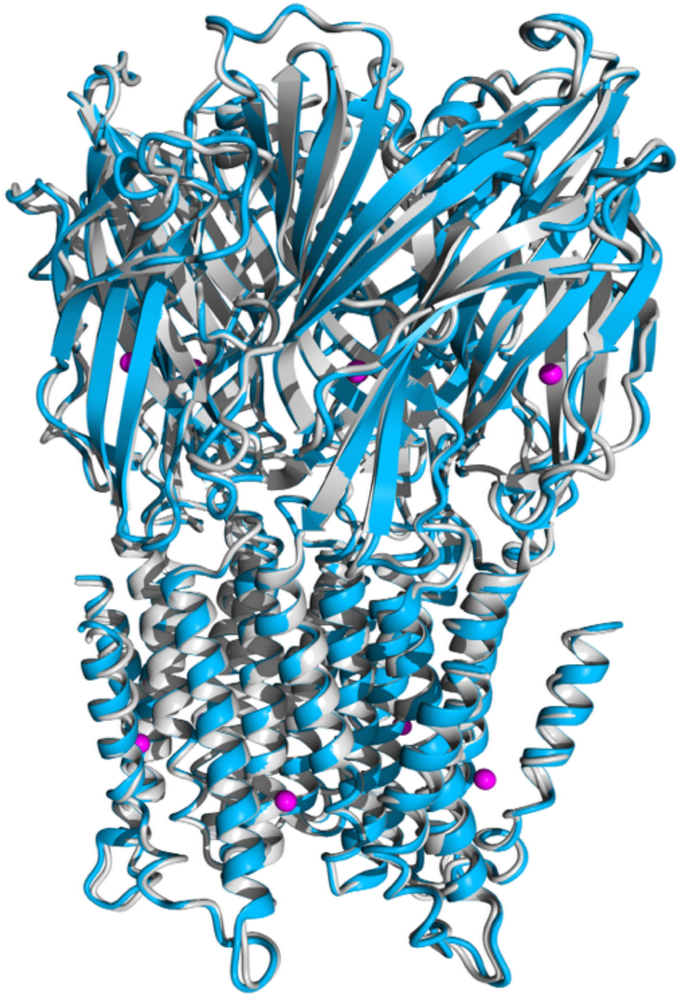
firefly luciferase

Nick Franks
(& Bill Lieb)

theories of anesthesia: receptors



the GABA-A receptor



the GABA-A receptor
+ Bromoform

Source: RSCB ID: 2VL0 and 3ZKR
Spurny, R. et al. (2013) J.Biol.Chem. 288: 8355

meta-theories of anesthesia

OLFACTION*

BY

L. J. MULLINS

Few physiological processes remain today as elusive of analysis and as obscure in mechanism as those involved in olfaction. Such a situation is not the result of any dearth of experimental investigations nor because of any reluctance on the part of physiologists to speculate concerning such mechanisms. Rather, we may suspect that our lack of a working hypothesis is to be traced to certain broad gaps in our knowledge of nervous excitation at both the physicochemical and the physiological level. The discussion that follows is not intended to do more than examine the areas of both physics and physiology to which we must look for explanations, and to consider the nature of the difficulties that arise in any attempt at a precise formulation of a theory of olfaction.

Recent reviews that very adequately summarize present-day knowledge of the histology of olfactory cells, the types of phenomena that have been observed, as well as the various theories of olfaction, are available and may be consulted for various details not presented here.[1-5] The olfactory cell is a primary neuron in contrast with the many specialized types of receptors that respond selectively to various physical stimuli. There are about 10 to 20 million such receptors in man[2] distributed over 5 cm.[2] of surface in the upper respiratory passages. This olfactory epithelium, as well as the rest of the nasal surface, also contains bare nerve fibers from the trigeminal nerve and these are generally considered as receptors which signal, by pain, the presence of many types of chemical compounds. The sensitive endings of the olfactory cell are a series of fine hairs (6 to 8 per cell in man, 10 to 14 in the rabbit) with dimensions about 2×0.1 microns. The endings of the olfactory cell are covered with a thin film of fluid, secreted by glands in the epithelium. Presumably this fluid is an ultrafiltrate of blood plasma. The fact that the nerve fibers emerging from olfactory receptors are short and nonmyelinated has discouraged any serious attempt to investigate the phenomena of olfaction by conventional electrophysiological methods. While it seems likely that, in the near future, technical improvements in neurophysiological technique will be such that direct recording in mammals will be possible, certain theoretical considerations, to be presented later, make the interpretation of such direct recording difficult.** One is faced,

*Aided by a grant (B-139) from the National Institute for Neurological Diseases and Blindness, United States Public Health Service, Bethesda, Md.

**Doctor Lloyd Beidler has advised me that he has been able to obtain direct recording in animals.

1954a

SOME PHYSICAL MECHANISMS IN NARCOSIS[1]

L. J. MULLINS

Biophysical Laboratory, Purdue University, Lafayette, Indiana

Received January 8, 1954

CONTENTS

I. INTRODUCTION

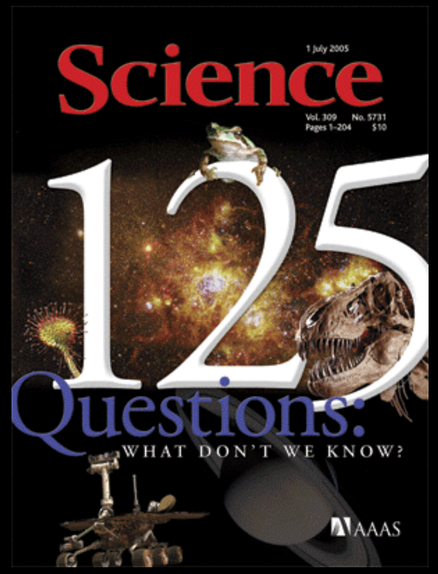
In 1920, Miller (42) offered an explanation of how the addition of 2 per cent sodium chloride to aqueous solutions of phenol increased the toxicity of the phenol for bacteria. His explanation was that the sodium chloride raised the chemical potential of the phenol in solution and hence, effectively, the escaping tendency of phenol toward bacteria. Unfortunately there was no generalization of this suggestion to include phenomena other than toxicity, and it remained for Ferguson (16) to show that the use of thermodynamic indices (chemical potential; activity) was helpful in predicting the aqueous concentrations of various substances that were necessary for toxicity and for narcosis. As will be seen later, the suggestion of Ferguson did not contribute any new information to the understanding of narcosis, but it did free the discussion of such phenomena from the artificiality of the Meyer–Overton hypothesis by showing that the partition coefficient, the vapor pressure of narcotics in solution, and various solubility relationships of narcotics are all derivable in principle from the thermodynamic activity. There is no argument that the concept of partition coefficients is im-

[1] This study has been aided by a grant from the Research Laboratories of Eli Lilly and Company.

1954b

Lorin Mullins 1917-1993

Lorin died after a short illness at his retirement home in Chestertown on April 14 [....]. He was working on a new theory of Anesthesia.



What is the nature of gravity?

It clashes with quantum theory. It doesn't fit in the Standard Model. Nobody has spotted the particle that is responsible for it. Newton's apple contained a whole can of worms.

How do general anesthetics work?

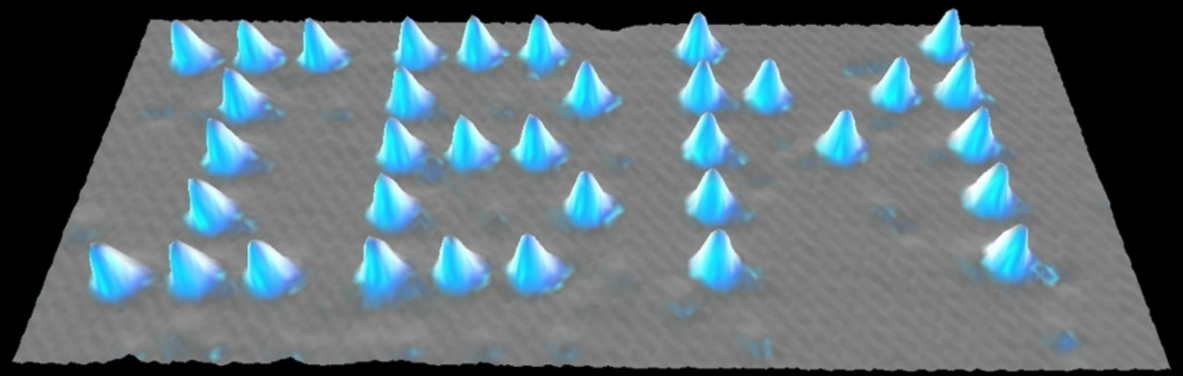
Scientists are chipping away at the drugs' effects on individual neurons, but understanding how they render us unconscious will be a tougher nut to crack.

Is ours the only universe?

A number of quantum theorists and cosmologists are trying to figure out whether our universe is part of a bigger “multiverse.” But others suspect that this hard-to-test idea may be a question for philosophers.

How do prion diseases work?

Even if one accepts that prions are just misfolded proteins, many mysteries remain. How can they go from the gut to the brain, and how do they kill cells once there, for example.



Imaging Xe with a Low-Temperature Scanning Tunneling Microscope

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IBM Research Division, Almaden Research Center, 650 Harry Road, San Jose, California 95120

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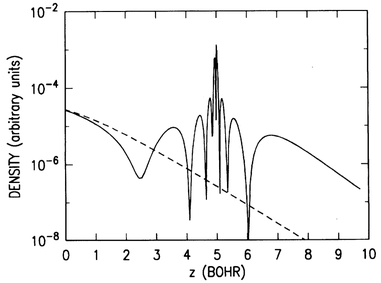
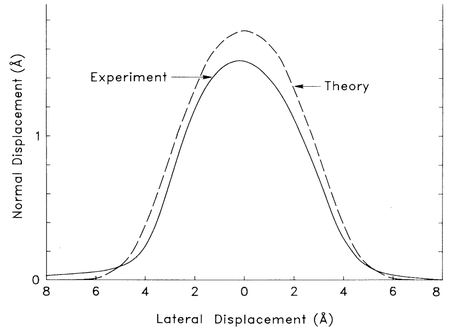


FIG. 2. The Fermi-level conduction-electron density along a normal to the surface through the nucleus of a Xe atom adsorbed at a distance of 5 bohrs from a metal modeled as $r_s = 2$ jellium (solid curve). The bare-metal density (dashed curve) is shown in order to emphasize the form and extent of the conduction-electron density redistribution. The conduction electrons extend further out into the vacuum at the Xe atom.



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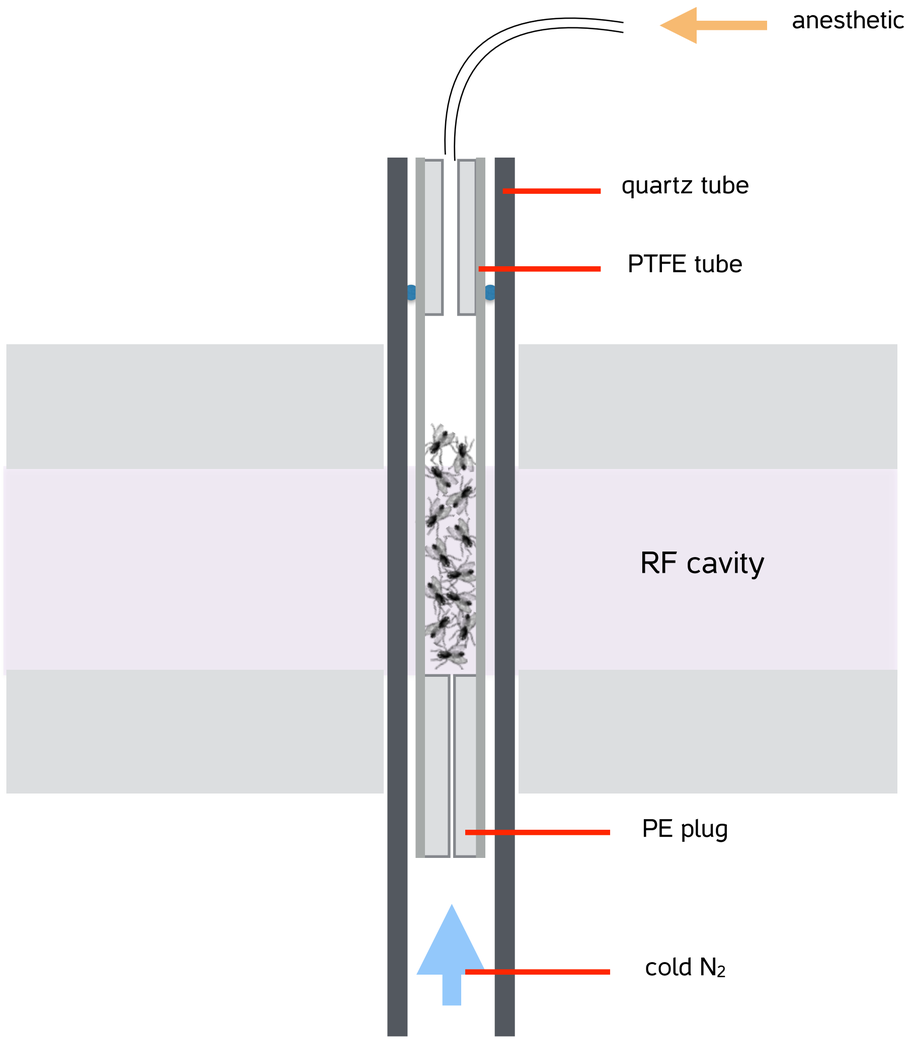
electron spin resonance [ESR] setup



melanin ESR

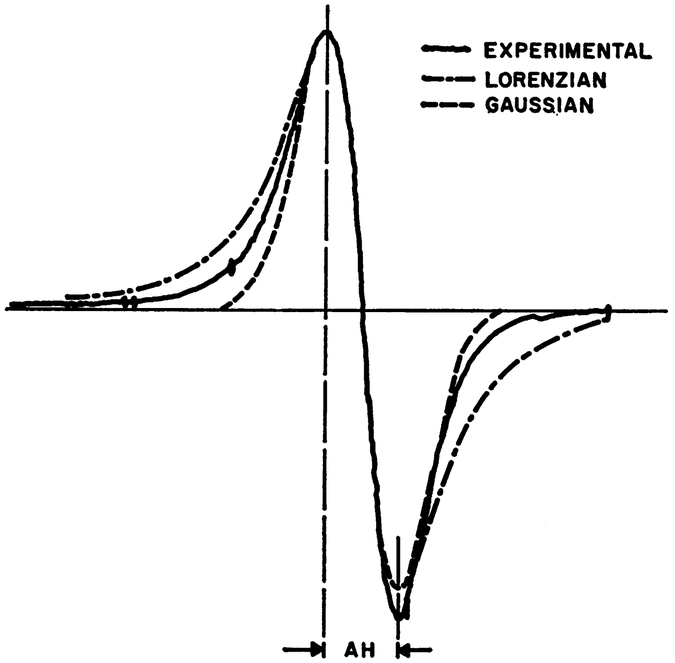
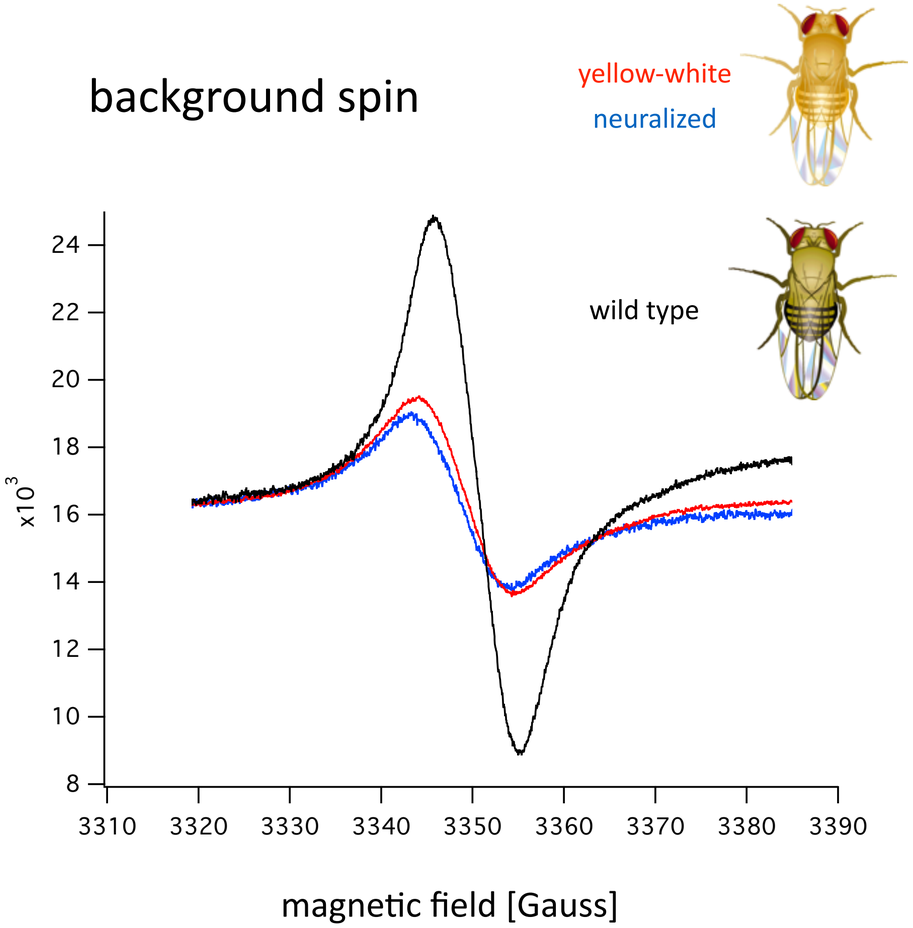
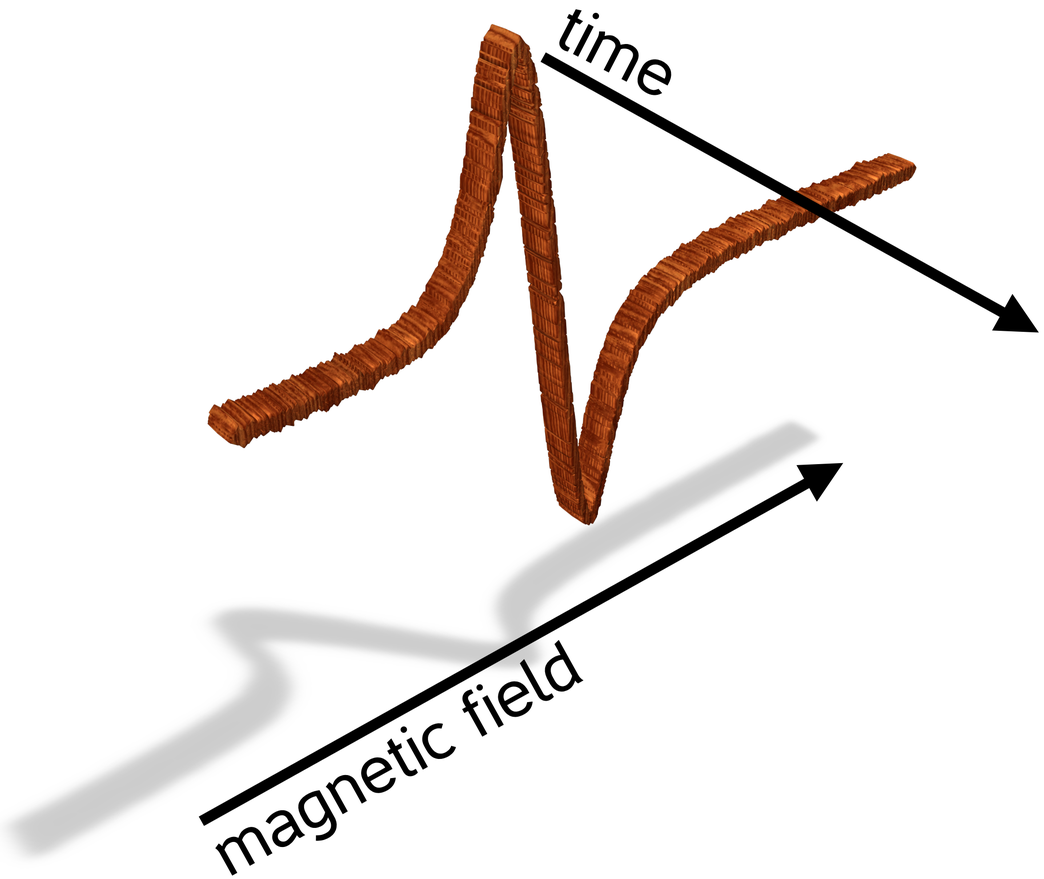


FIGURE 2 The e.s.r. absorption of squid melanin (first derivative trace).

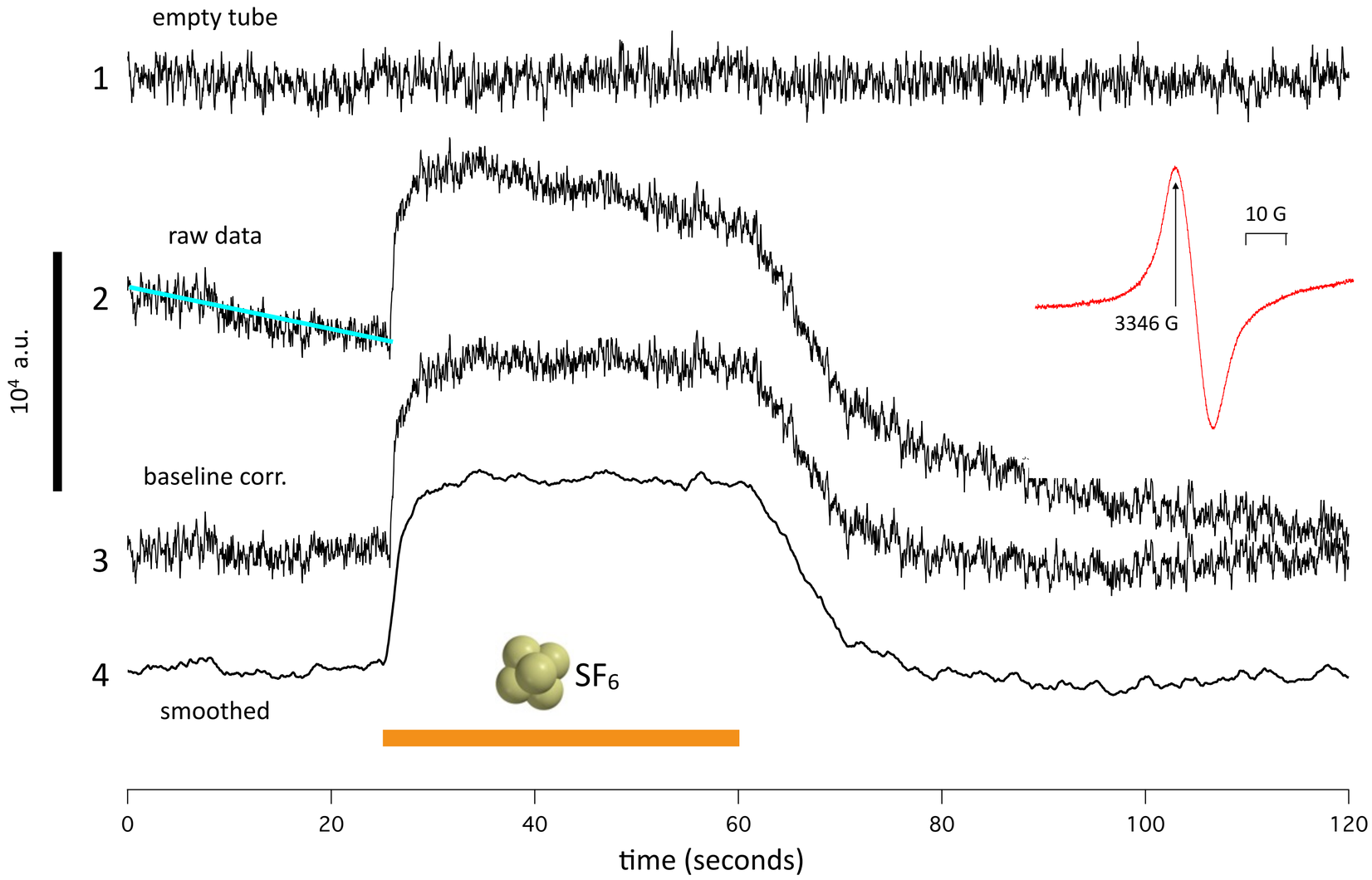
Blois, Zahlan and Maling, Biophys J 4:471 (1964



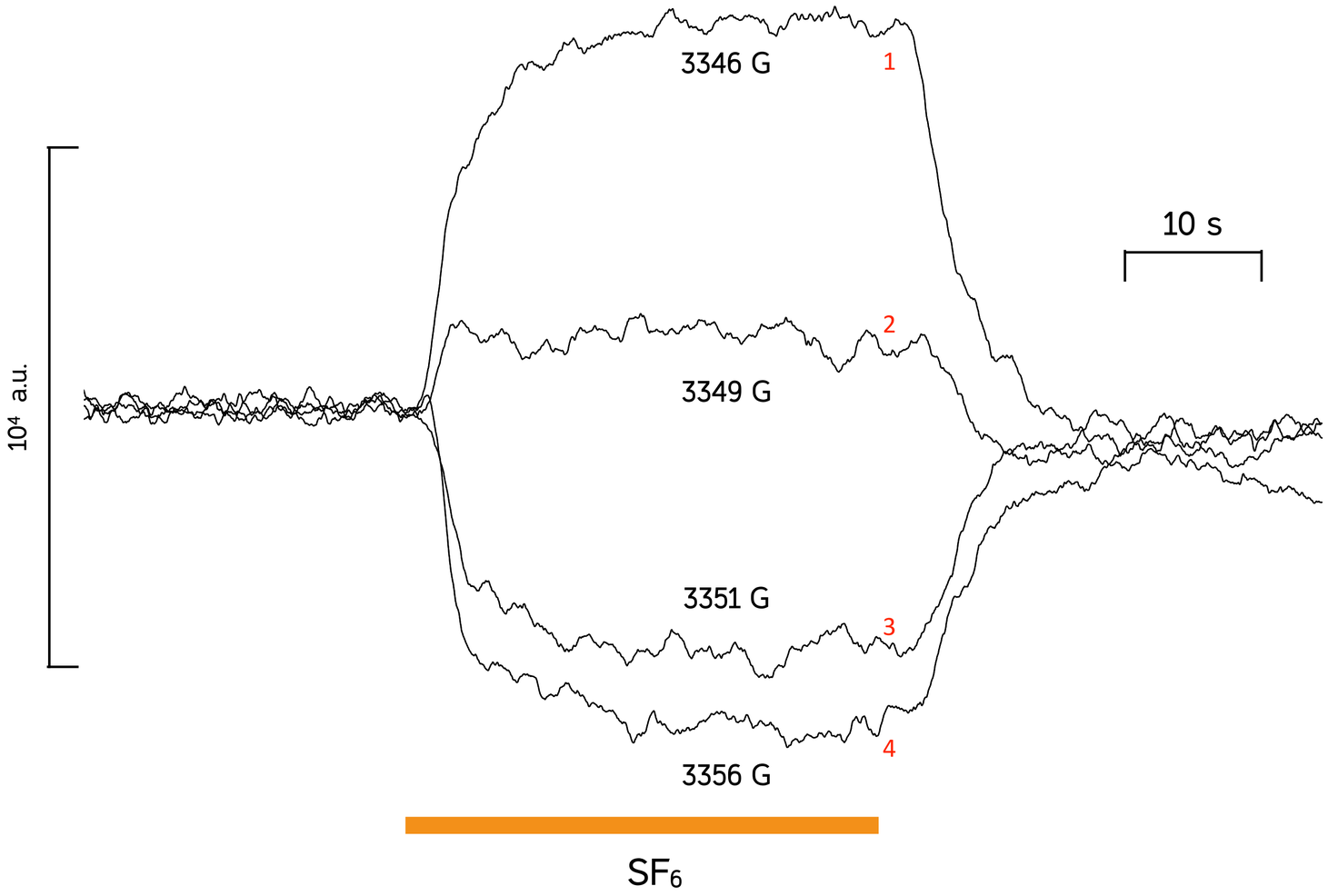
two types of ESR measurement

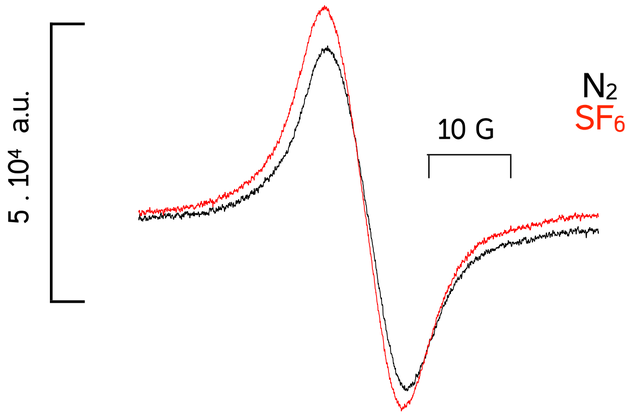


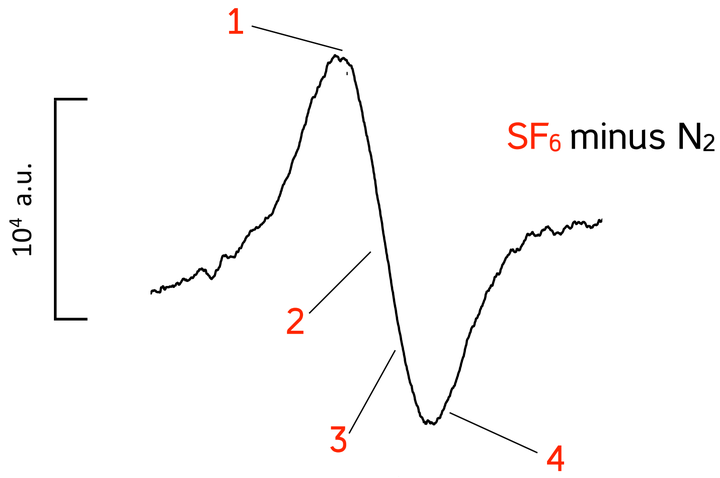
spin changes during SF_6 anesthesia



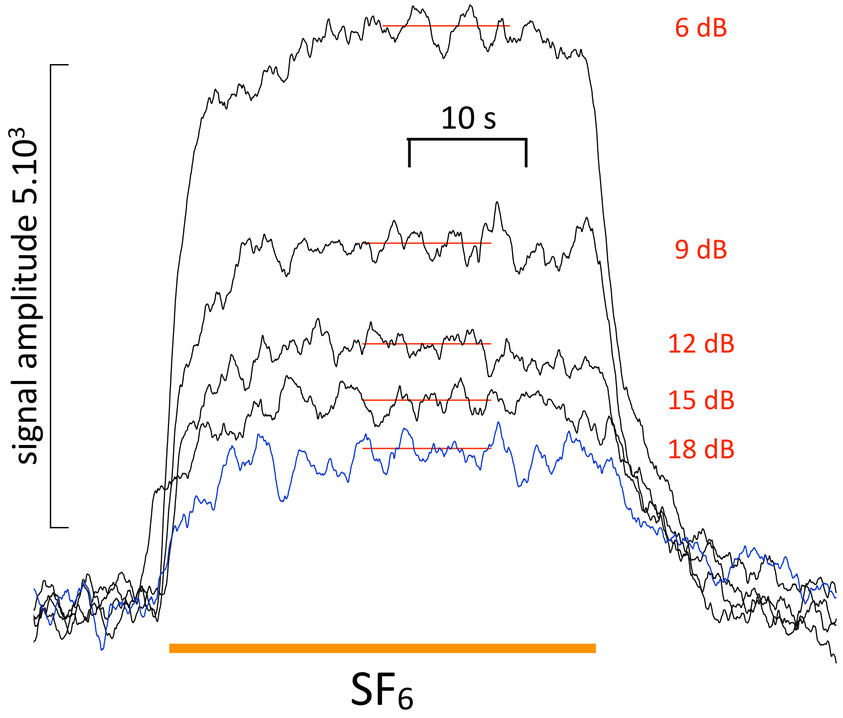
spin change depends on magnetic field value

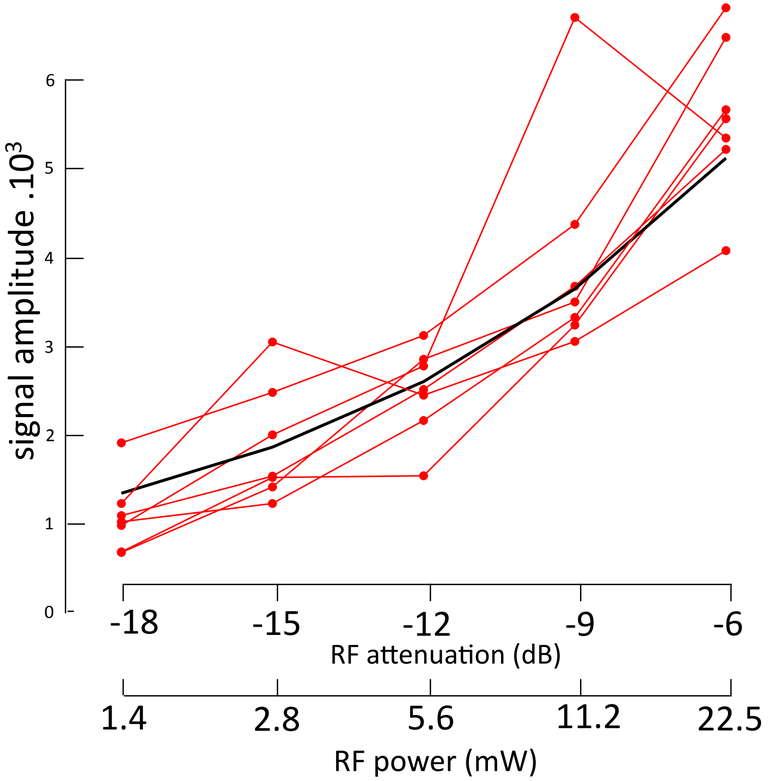




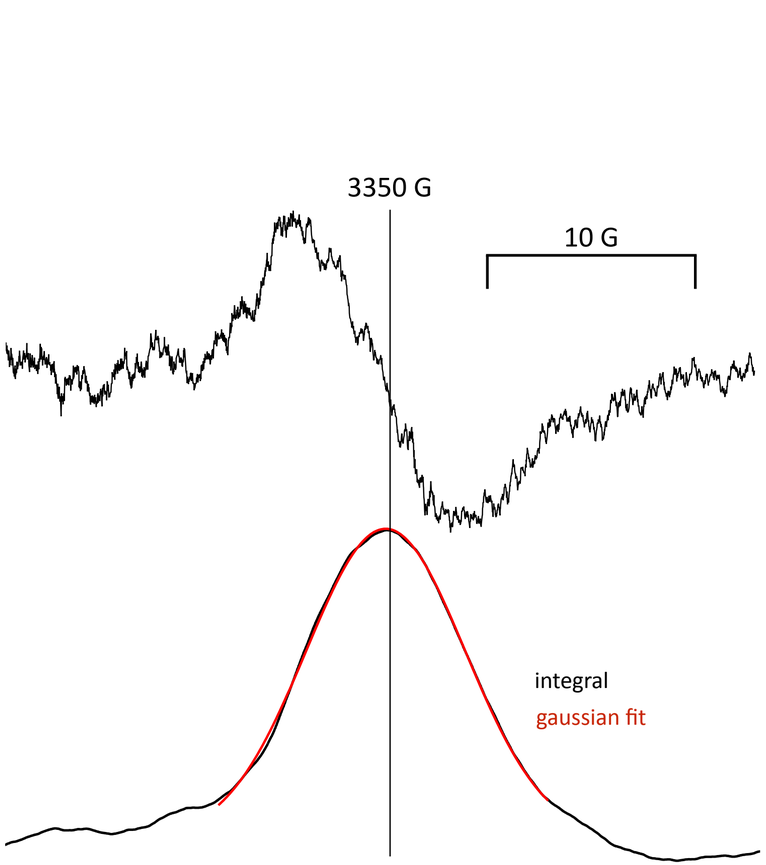


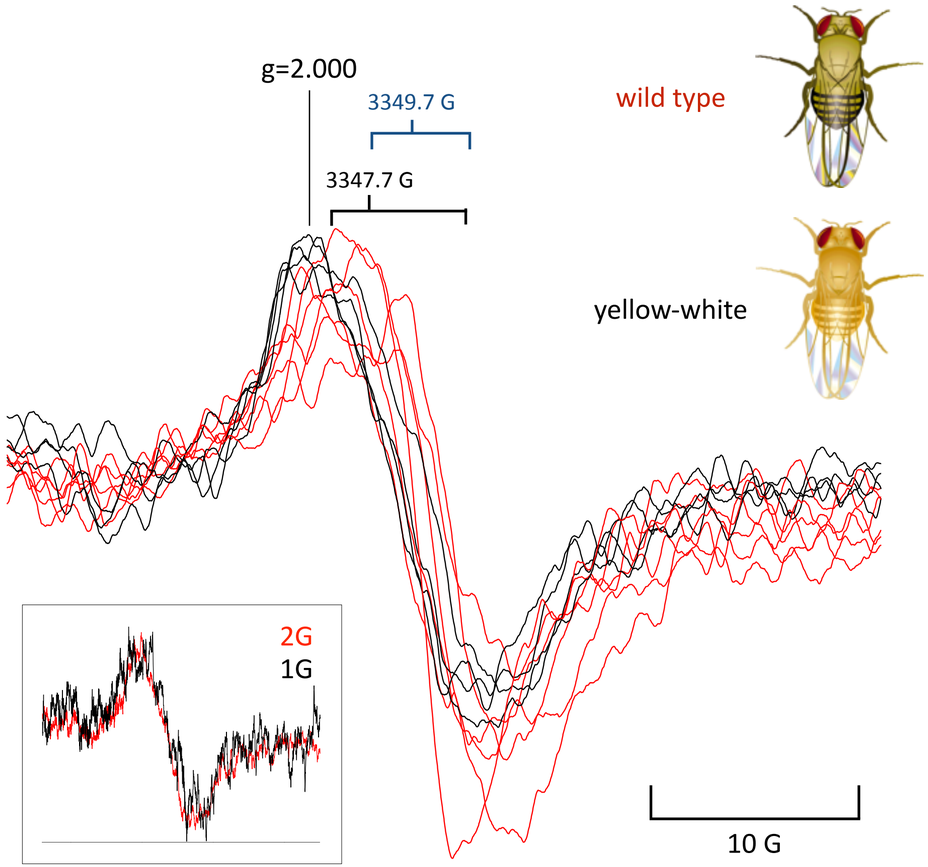
saturation behaviour of anesthetic signal



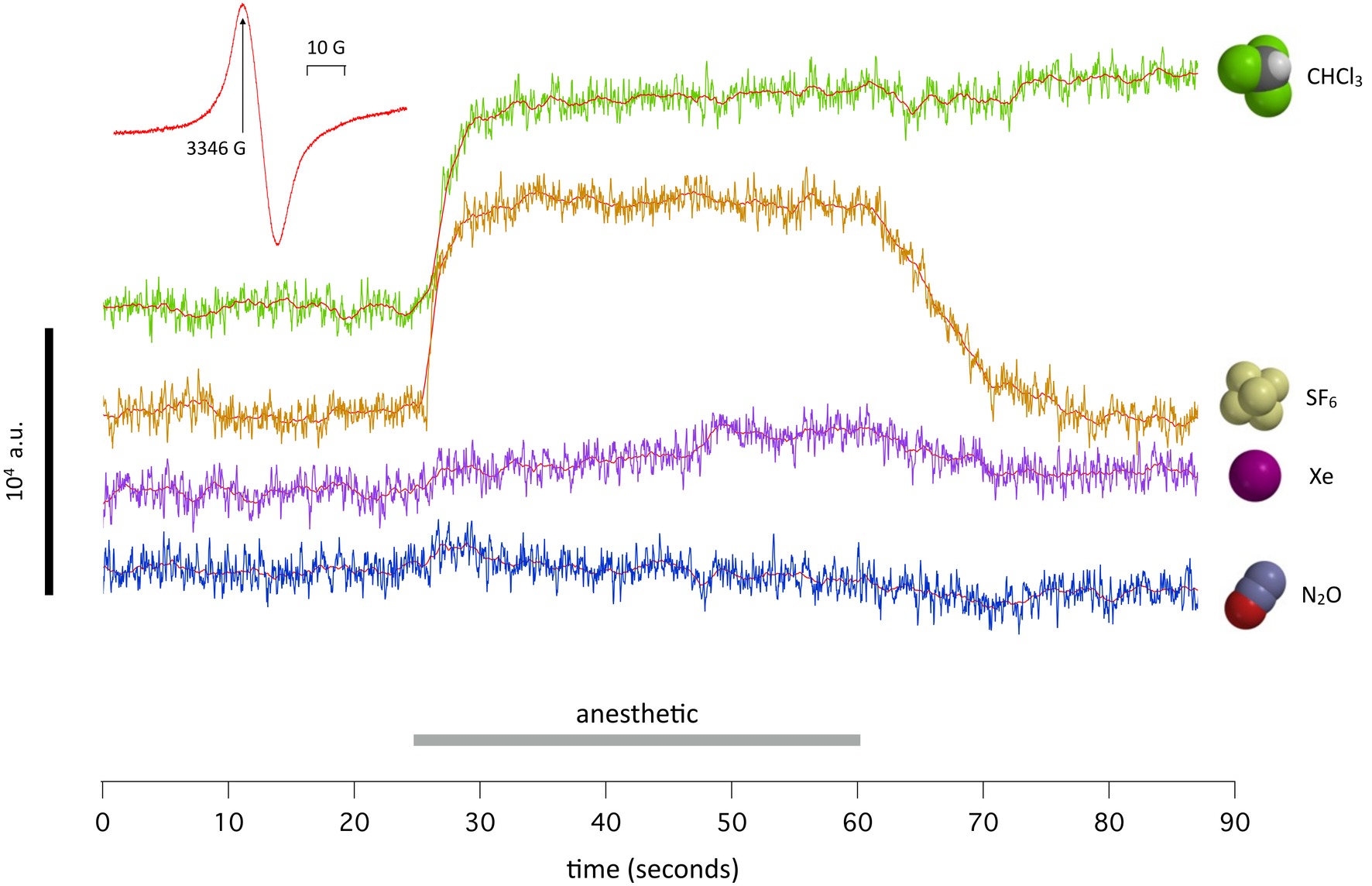


anesthetic signal size is independent of eumelanin

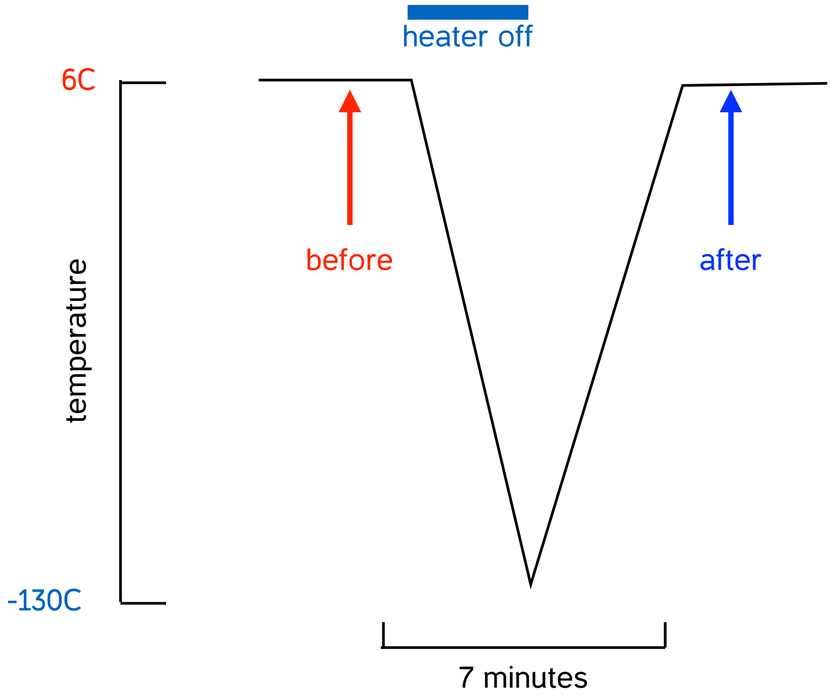


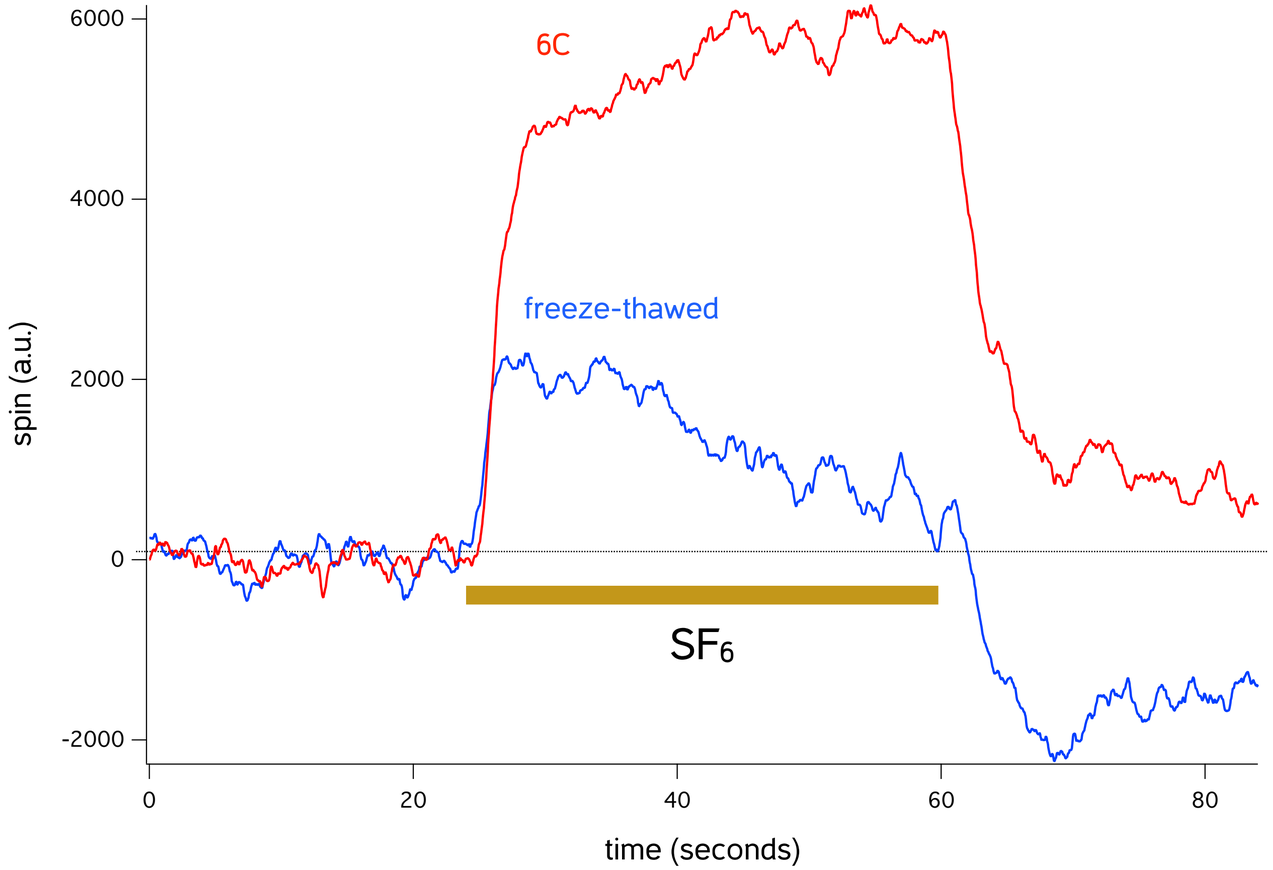


spin changes with different anesthetics

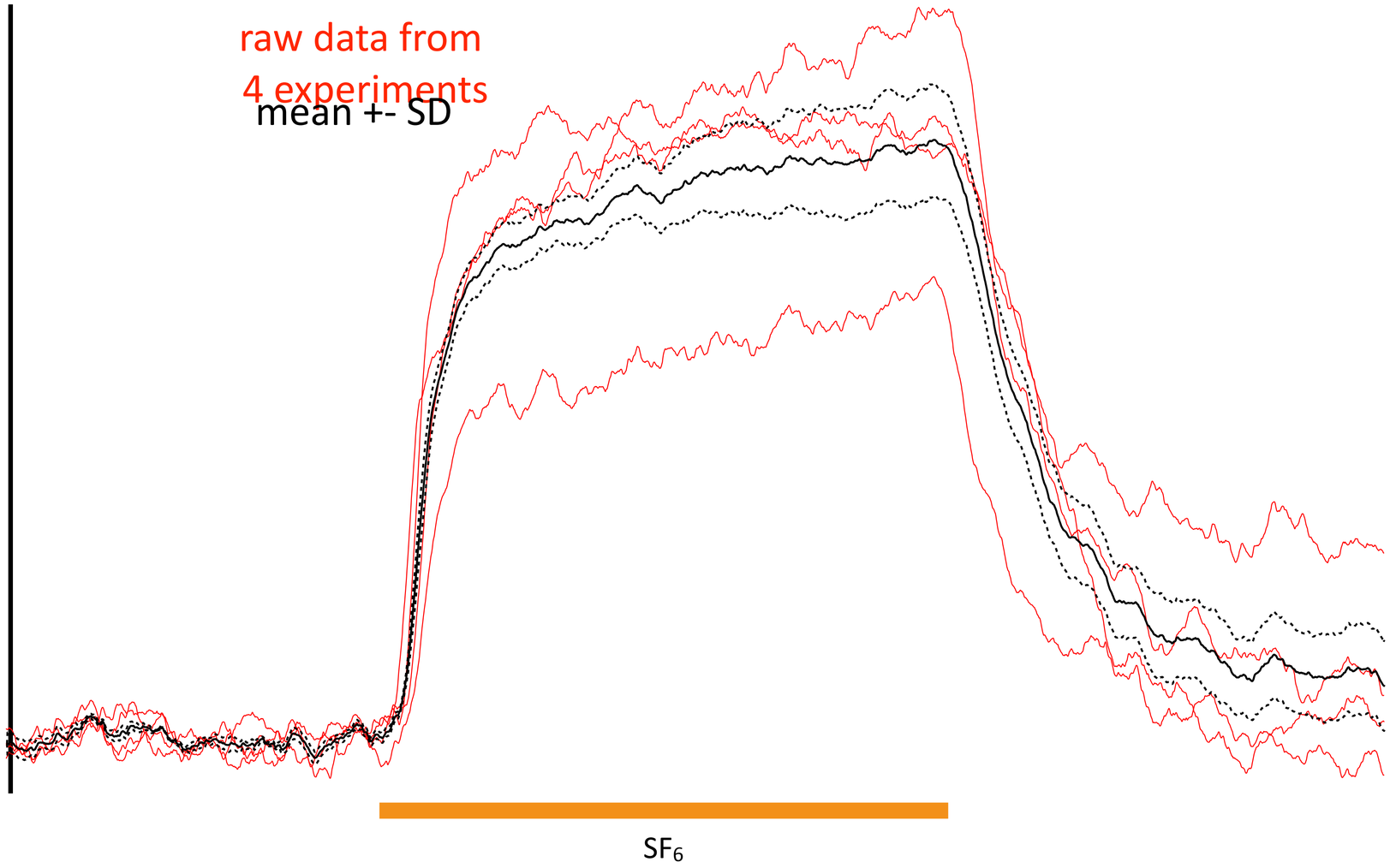


effect of freeze-thaw on anesthetic signal

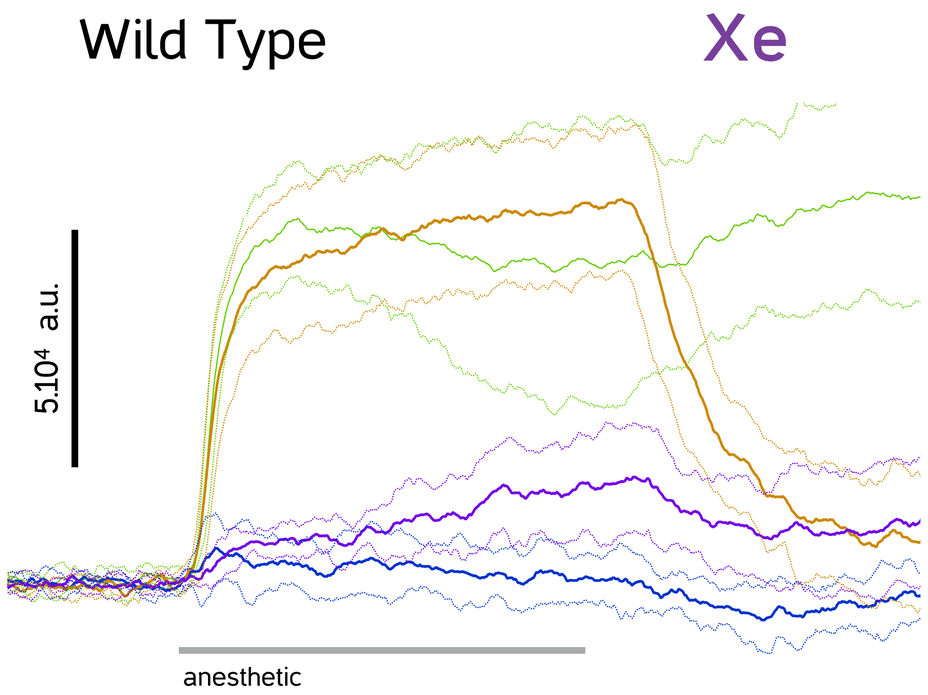


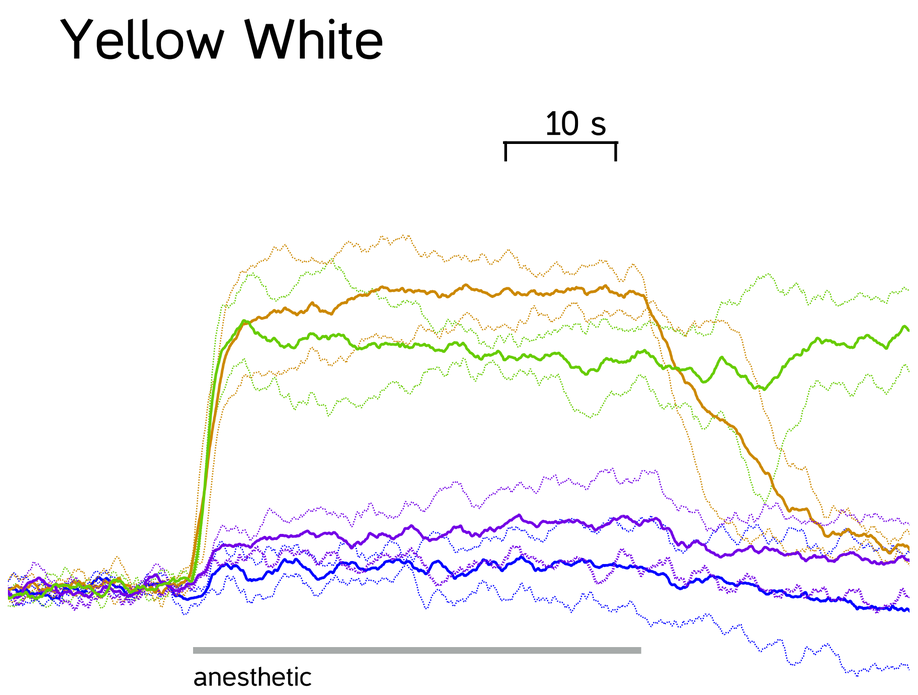


data processing for analysis



control responses to general anesthetics

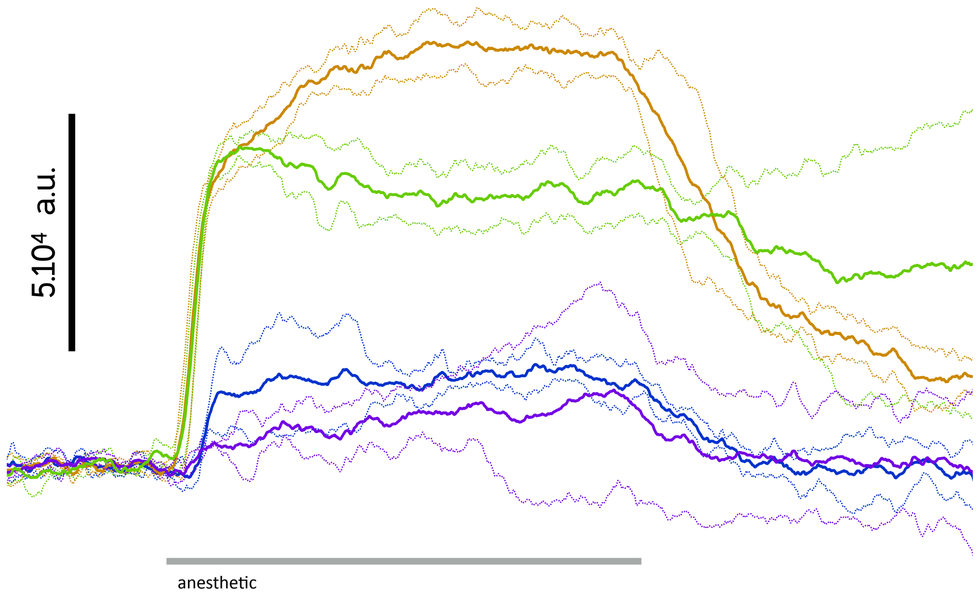




mutant responses to general anesthetics 1/3

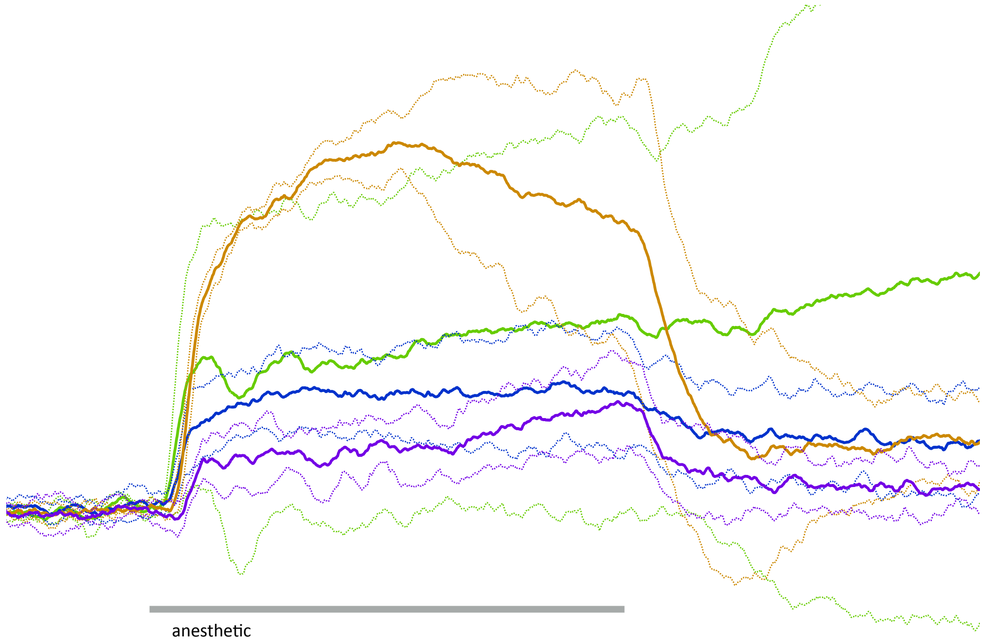
ion channel mutant

HAR85 N_2O



halothane resistant

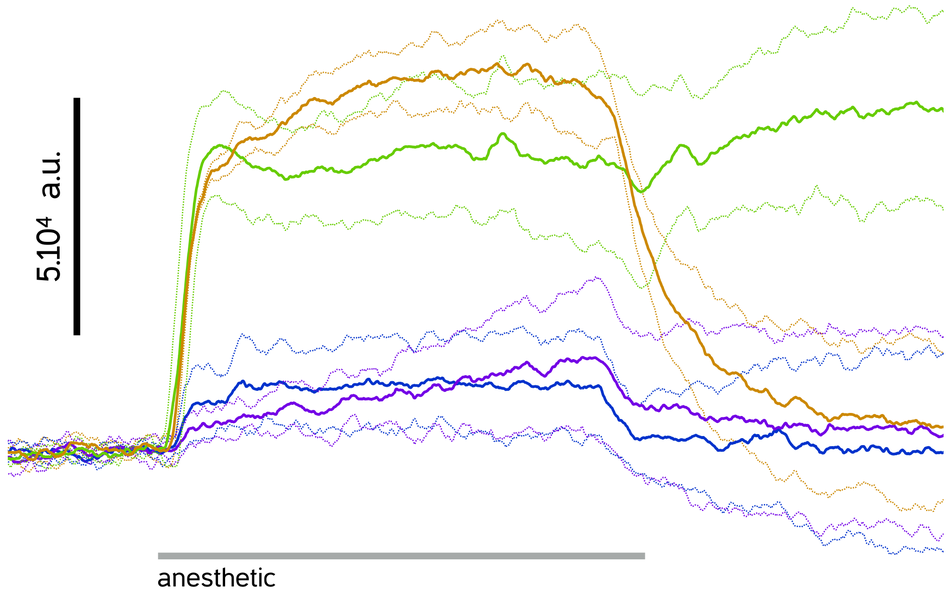
AGAR11 N_2O Xe awake



mutant responses to general anesthetics 2/3

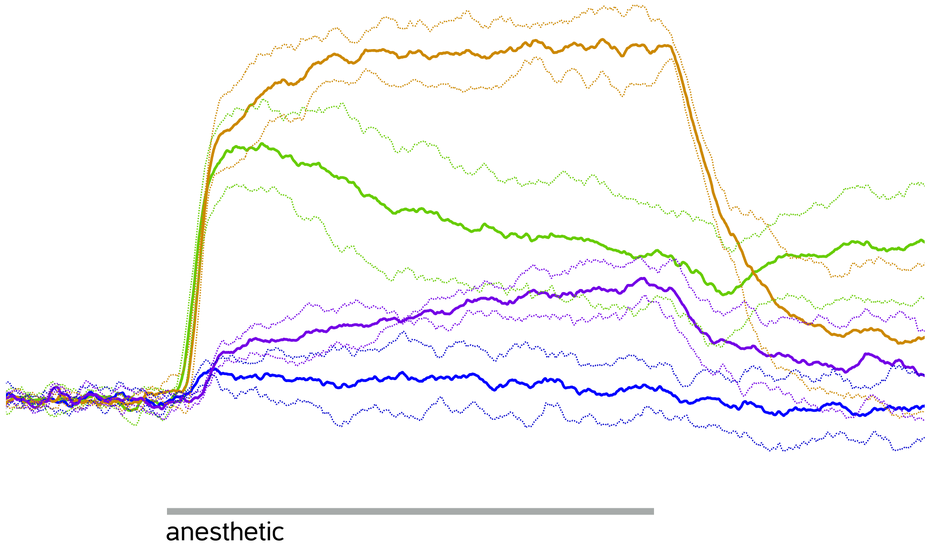
halothane resistant

AGAR53 **awake**



halothane resistant

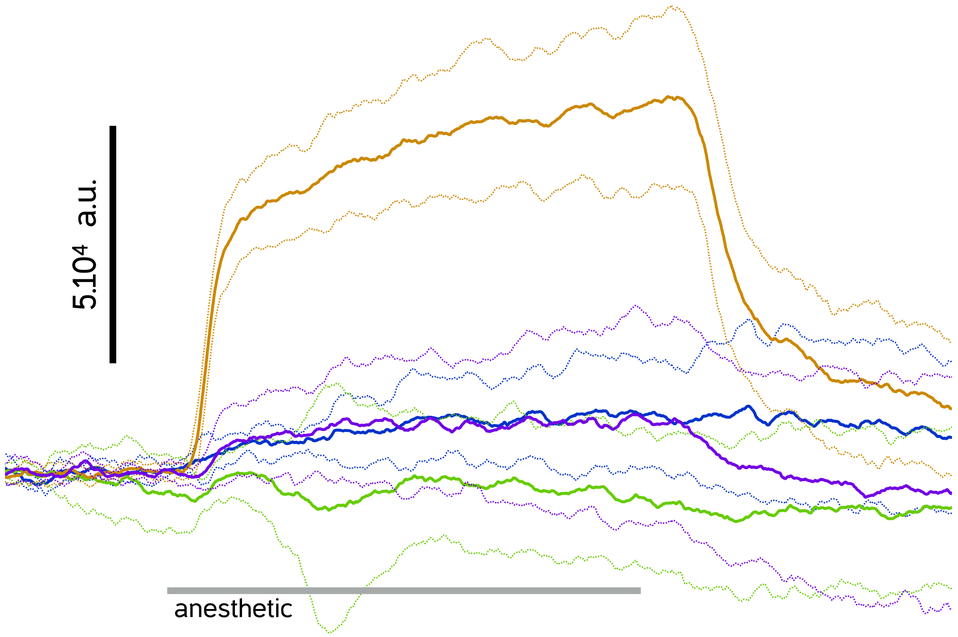
AGAR211 small CCl_3 Xe



mutant responses to general anesthetics 3/3

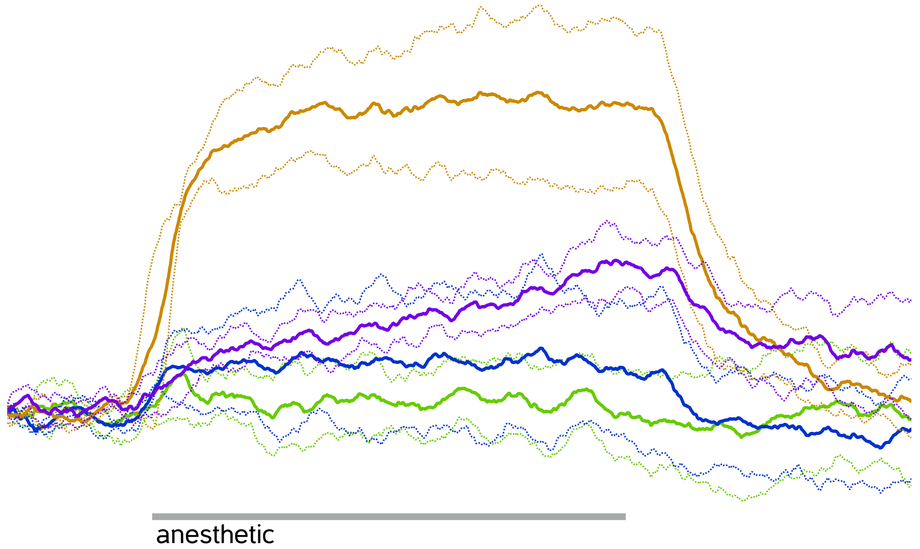
halothane resistant

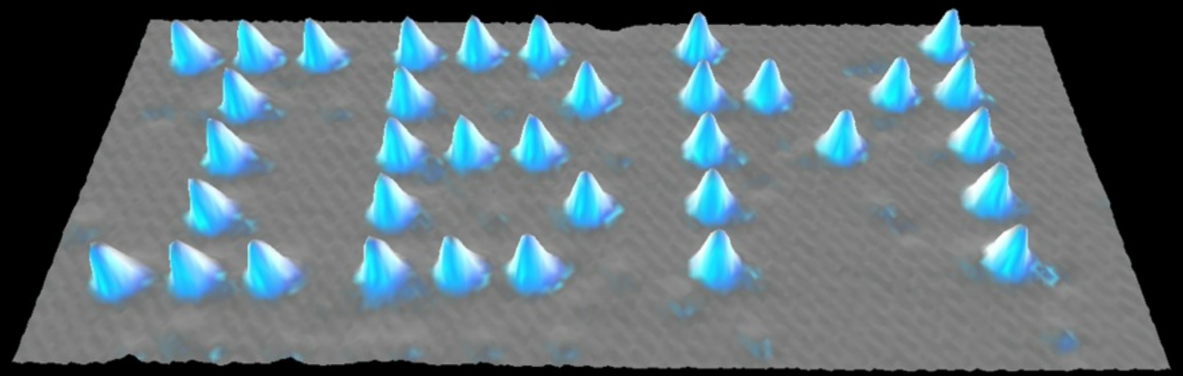
AGAR21 no CCl_3 awake



halothane resistant

AGAR52 no CCl_3 Xe awake





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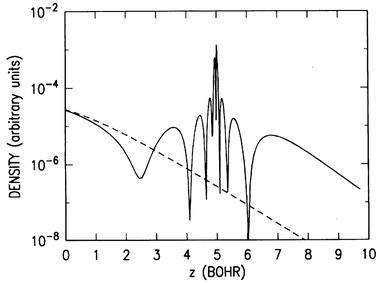

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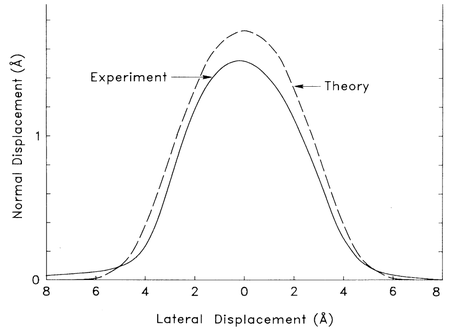

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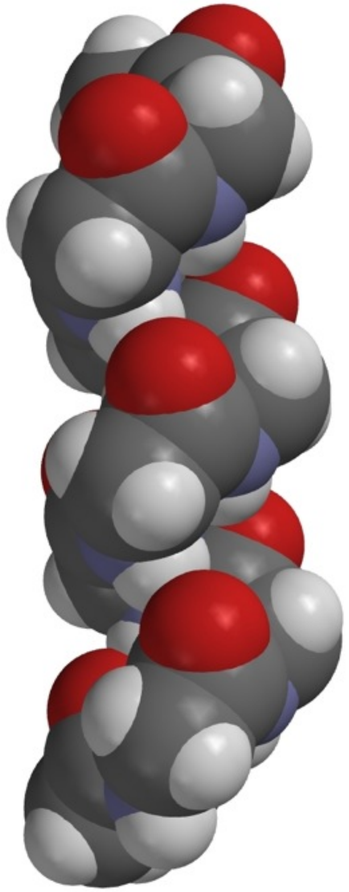
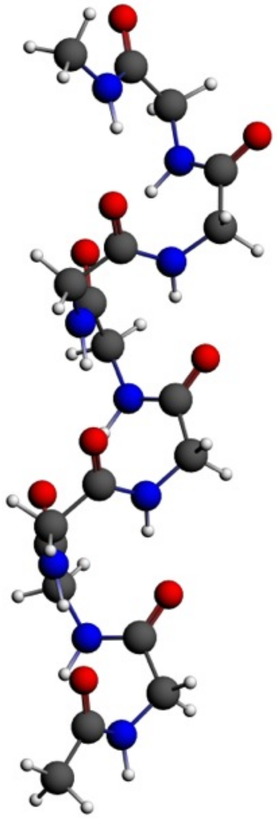
CH_3-terminated 5-gly alpha helix

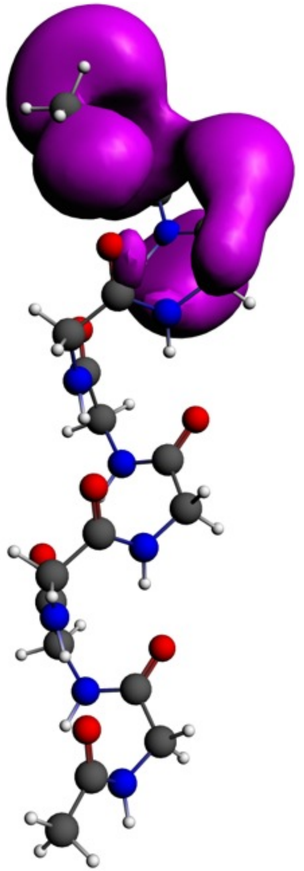
VdW radii



ball and stick



HOMO*

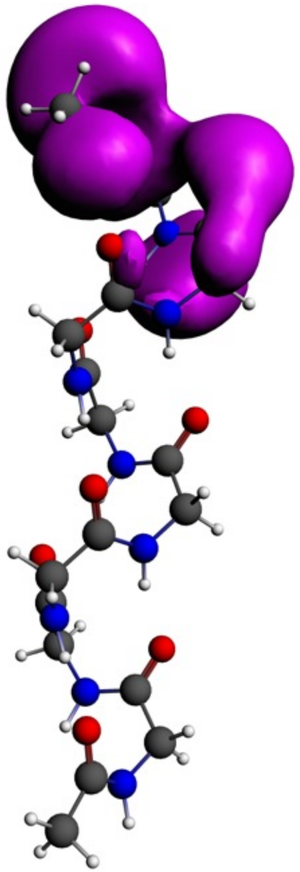


*Highest Occupied Molecular Orbital

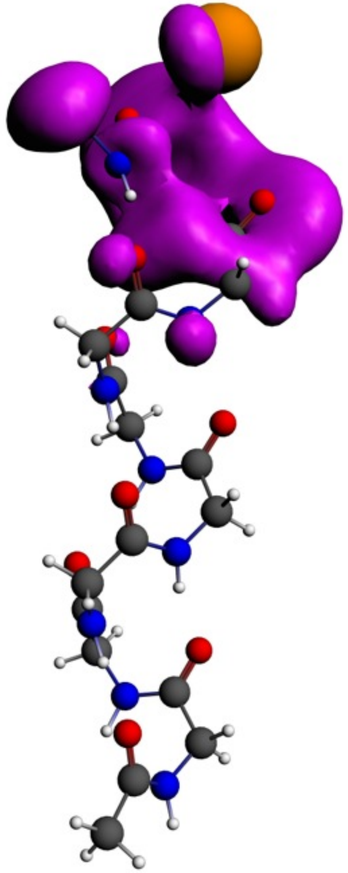
PBE-DZP minimization, B3LYP single point

effect of anesthetics on helix HOMO

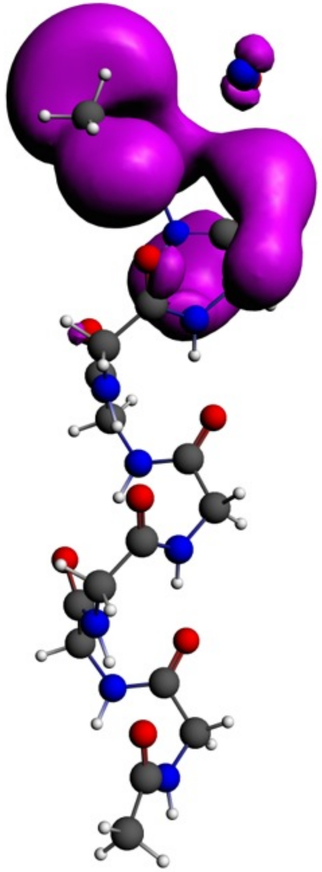
vacuum



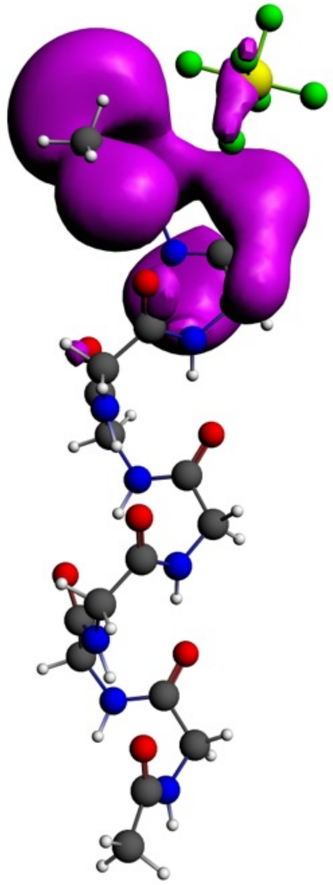
Xe



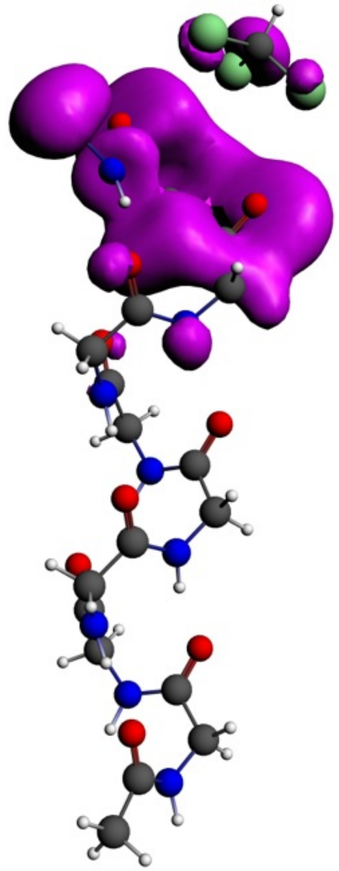
N_2O



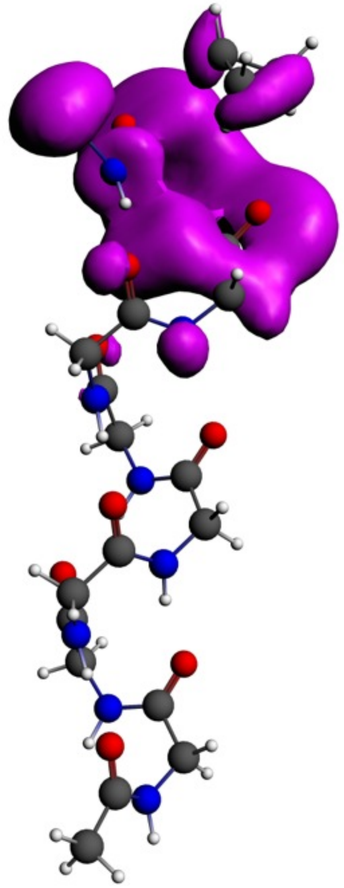
SF_6



$CHCl_3$

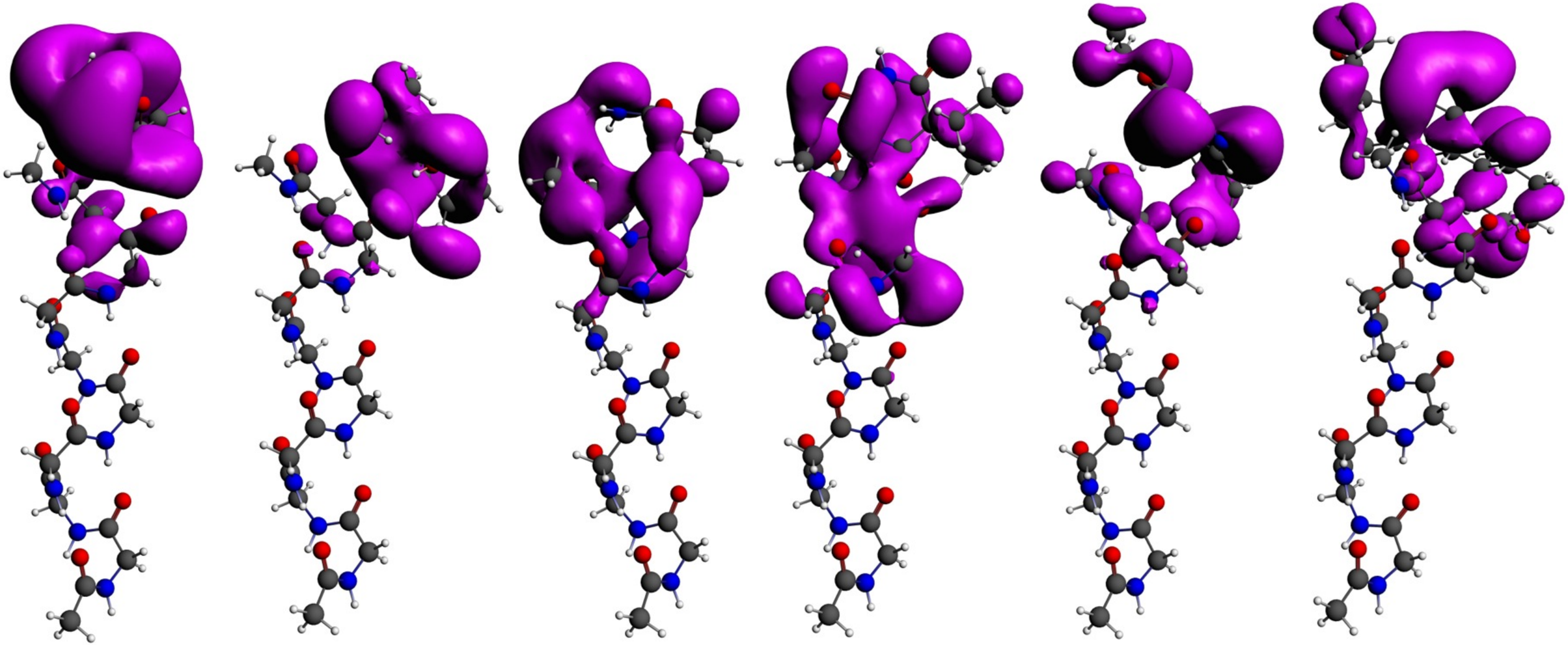


C_3H_6



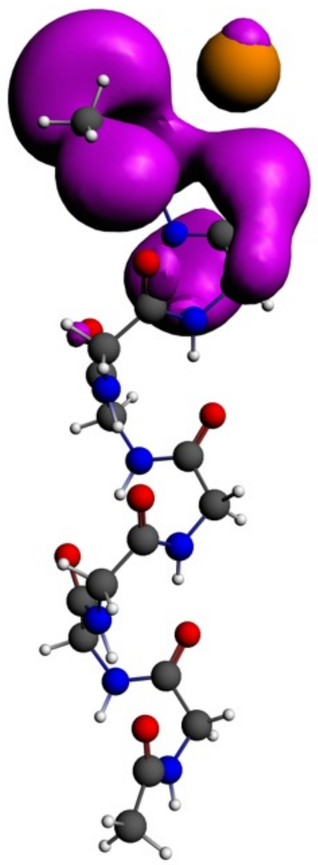
effect of anesthetics on helix HOMO

ether propofol urethane barbital etomidate alfaxalone

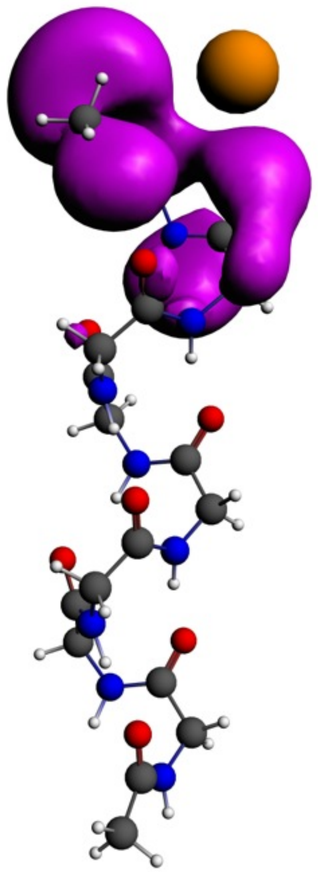


effect of diving gases on helix HOMO

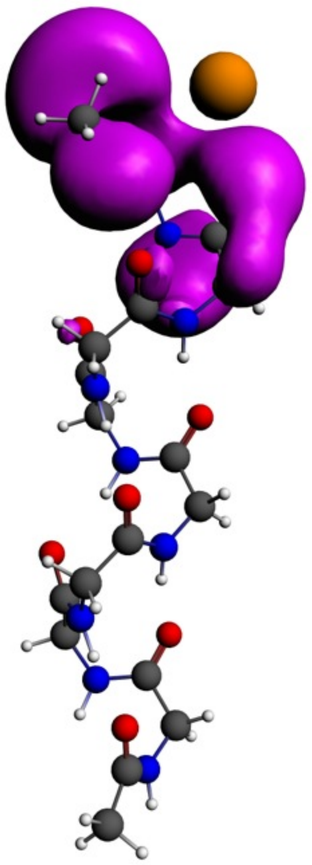
Kr



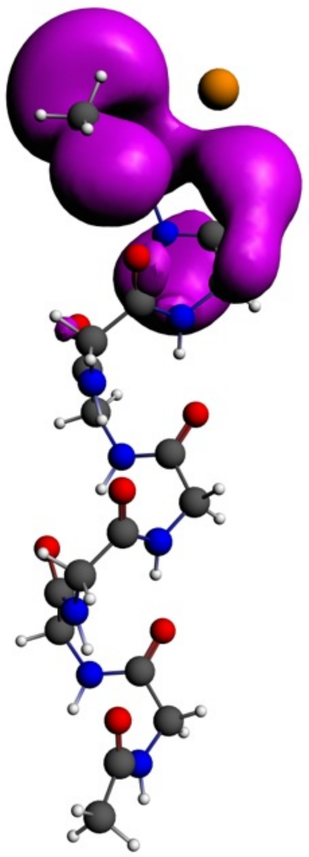
Ar



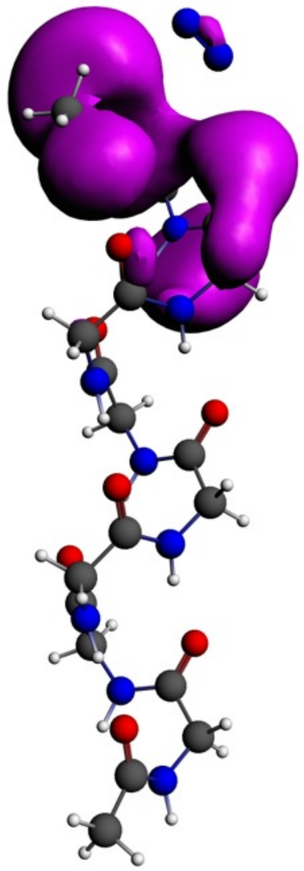
Ne



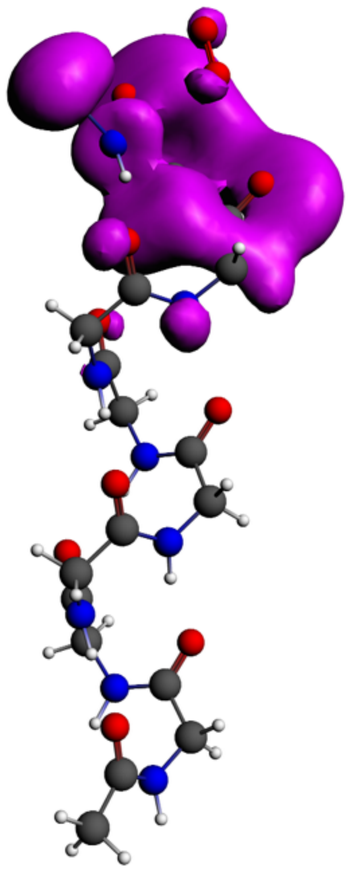
He



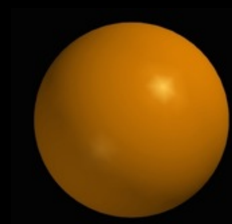
N_2



O_2



Così Fan Tutti



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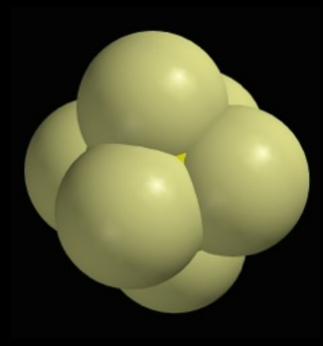
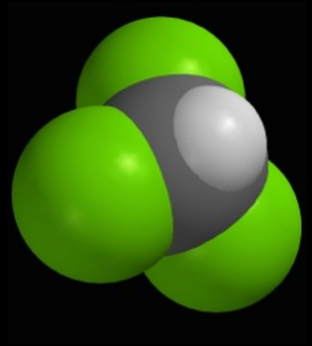
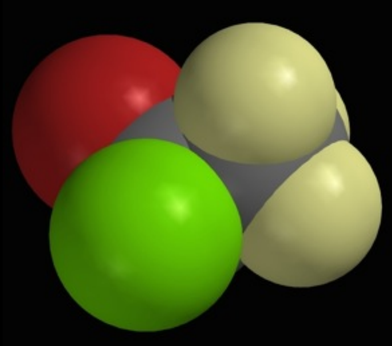


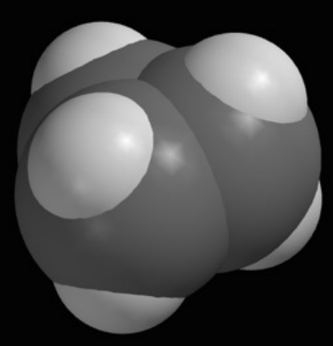
SF_6



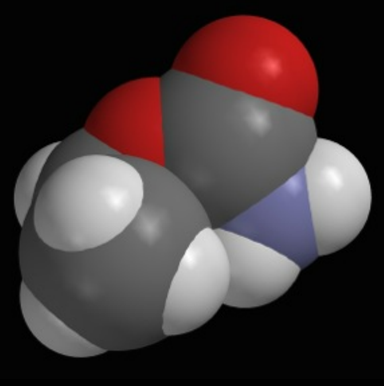
$CHCl_3$



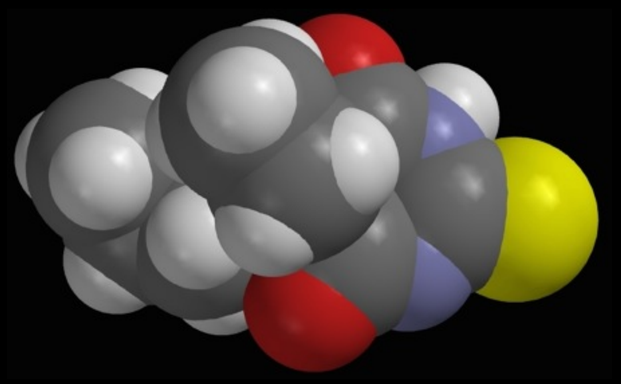
halothane



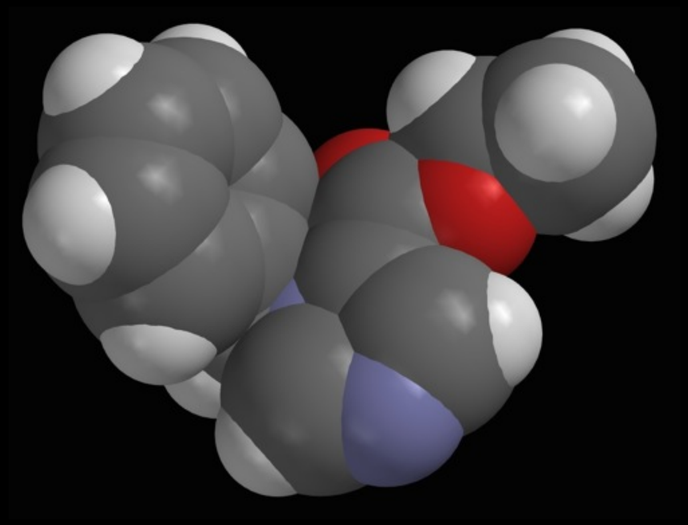
cyclopropane



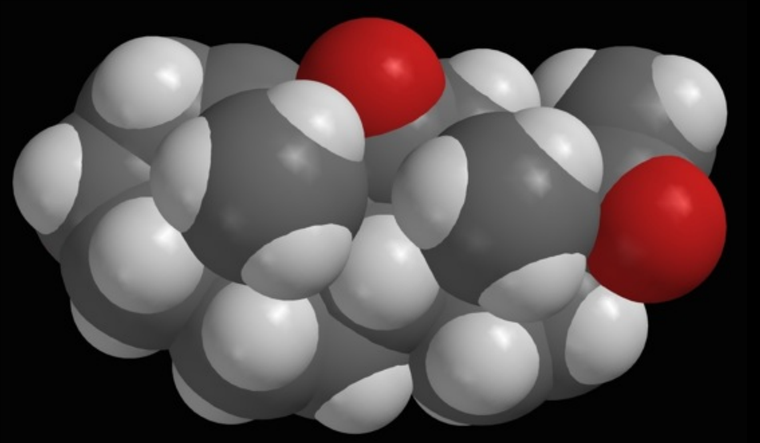
urethane



thiopental



etomidate



alfaxalone

in conclusion

- general anesthetics cause a change in electron spin
- which is sometimes absent or different in resistant mutants
- they all perturb the electronic structure of proteins

Landauer Limit: kT ln2 or ~ 18 meV at 300K

ATP hydrolysis energy: ~ 600 meV ~ 33 times LL

Anesthetic-sensitive energy consumption of 1 g of brain~ 10 mW or

$\sim 10^{17}$ bits/s

10^8 neurons/g, so per neuron

10^9 bits/sec as opposed to current 10^3

Thank You