Can a microscopic stochastic model explain the emergence of pain cycles in patients?

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Pain mechanism

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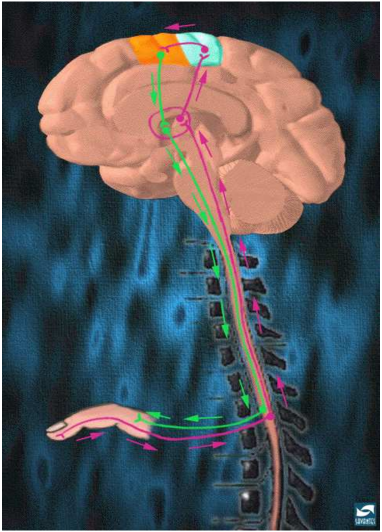
- This activity is initiated by nociceptors, or pain receptors, that can detect mechanical, thermal or chemical changes, above a set threshold
- Once stimulated, a nociceptor transmits a signal along the spinal cord, to the brain



Analgesics

An analgesic is any member of the diverse group of drugs used to relieve pain (achieve analgesia). Analgesic drugs act in various ways on the peripheral and central nervous systems

Analgesics are commonly used in basic research and clinical practice but the molecular mechanisms regulating their functions remain to be fully elucidated

Markers of Pain

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Evoked Response Potentials (ERPs)

The rodent whisker sensory system

- Adult rats
- Electrode array placed on the surface of the somatosensory cortex
- Administration of different anesthetics
- Whisker stimulation
- Record of ERP

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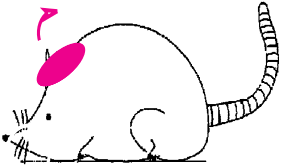

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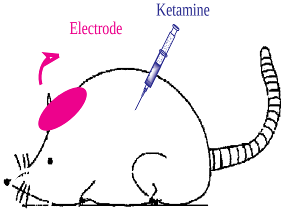

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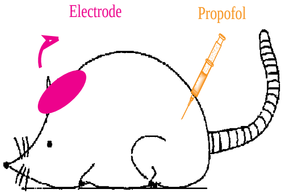

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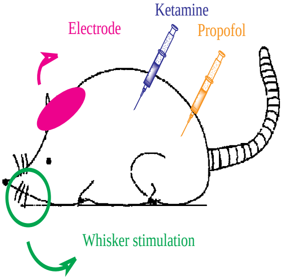

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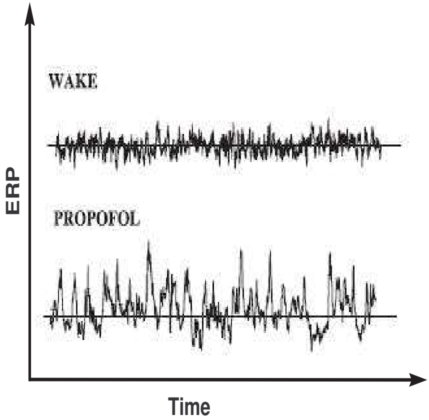
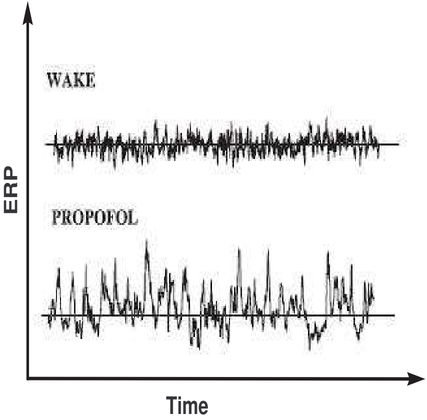


Rojas et Al, Am J Physiol Regul Integr Comp Physiol, 2006(291), R189-R196

The rodent whisker sensory system

- Understanding these signals is an **open problem**
- We shall hereon speculate on the **role of noise** which is intrinsic to the system at hand in the aim of providing a possible interpretative framework



Question

- Why do these oscillations exist?
- Is there a molecular interpretation for their emergence?

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A stochastic model

- interaction between the anesthetics and the target receptors
- presence of diverse chemical species
- pain receptors act as effective gates regulating the transmission of pain

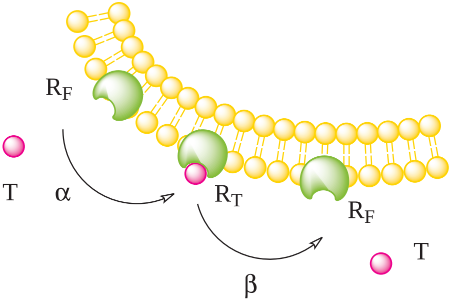
Essential mechanisms

- Binding process

$$T + R_F \xrightarrow{\alpha} R_T + E$$

- Spontaneous detachment

$$R_T + E \xrightarrow{\beta} T + R_F$$



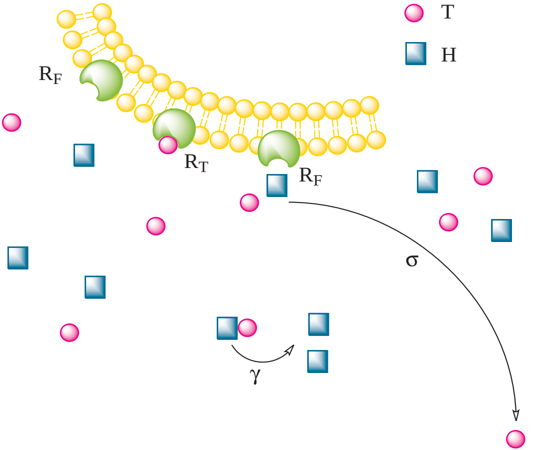
Competition

- Collision

$$H + T \xrightarrow{\sigma} H + E$$

- Transformation

$$H + T \xrightarrow{\gamma} H + H$$



Diffusion

$$T \xrightarrow{\delta_1} E$$

$$E \xrightarrow{\eta_1} T$$

$$H \xrightarrow{\delta_2} E$$

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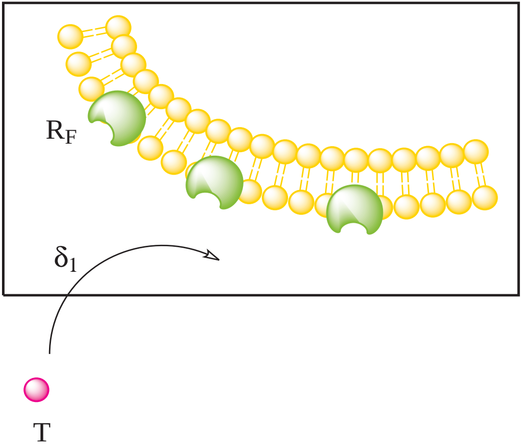

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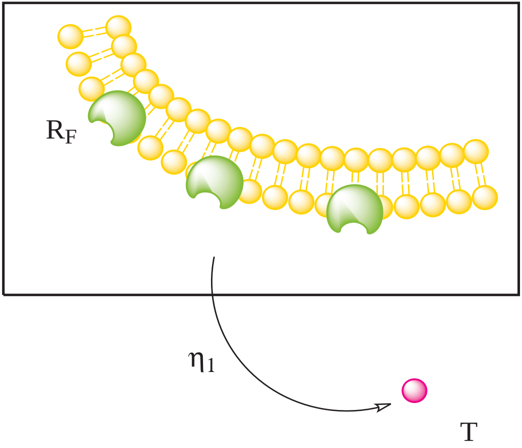


Diffusion

$$T \xrightarrow{\delta_1} E$$

$$E \xrightarrow{\eta_1} T$$

$$H \xrightarrow{\delta_2} E$$

$$E \xrightarrow{\eta_2} H$$

The complete model

$$T + R_F \xrightarrow{\alpha} R_T + E$$

$$R_T + E \xrightarrow{\beta} T + R_F$$

$$H + T \xrightarrow{\gamma} H + H$$

$$H + T \xrightarrow{\sigma} H + E$$

$$T \xrightarrow{\delta_1} E$$

$$E \xrightarrow{\eta_1} T$$

$$H \xrightarrow{\delta_2} E$$

$$E \xrightarrow{\eta_2} H$$

- $N_1 = n_{R_T} + n_{R_F}$
- $N_2 = n_T + n_H + n_E$

- $n_{R_F} = N_1 - n_{R_T}$
- $n_E = N_2 - n_T - n_H$

$$\underline{n} = (n_T, n_{R_T}, n_H)$$

Gillespie algorithm

The Gillespie algorithm allows a discrete and stochastic simulation of a system with a finite number of reactants because every reaction is explicitly simulated

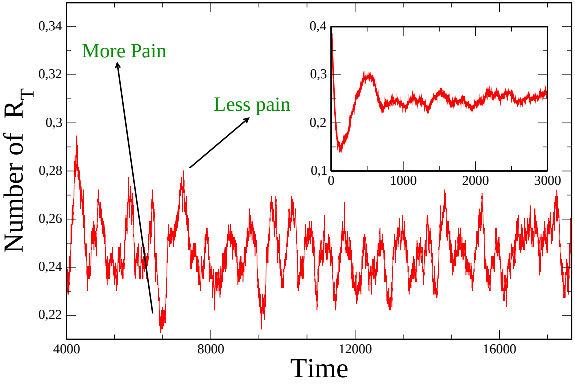
Steps:

0 Initialization: Initialize the number of molecules in the system, reactions constants, and random number generators

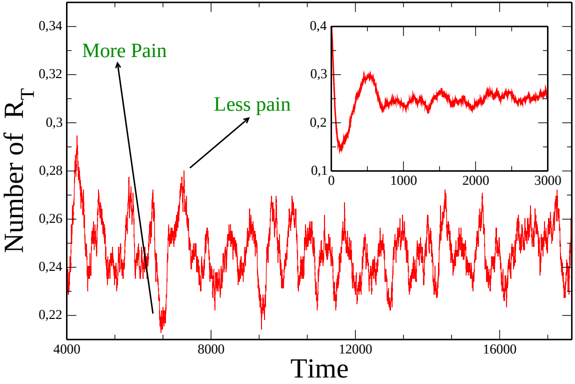
1 Monte Carlo Step: Generate random numbers to determine the next reaction to occur as well as the time interval

2 Update: Increase the time step by the randomly generated time in step 1. Update the molecule count based on the reaction that occurred

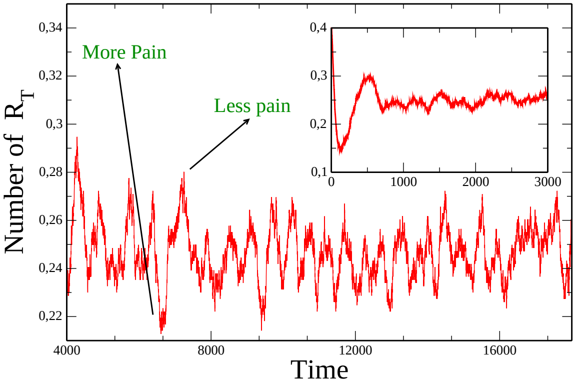
3 Iterate: Go back to step 1 unless the simulation time has been exceeded



More Pain
Less pain
Number of R_T
Time
0,34
0,32
0,3
0,28
0,26
0,24
0,22
4000
8000
12000
16000
0,4
0,3
0,2
0,1
0
1000
2000
3000



Large (resp. small) n_{R_T} correspond to a less (resp. more) pronounced electrical activity



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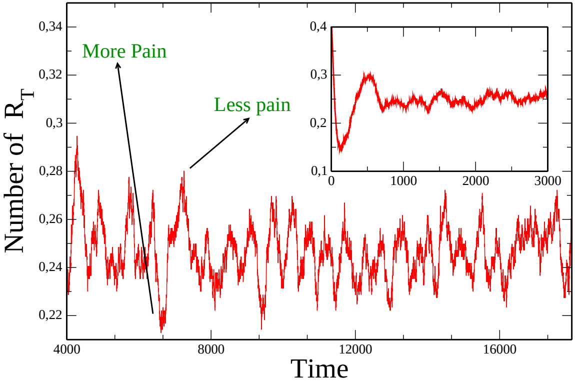
PAIN $\leftrightarrows$ ERPs



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PAIN ⇆ ERPs

Transition Probabilities

$$T + R_F \xrightarrow{\alpha} R_T + E$$

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$$T(n_T - 1, n_{R_T} + 1, n_H | \underline{n})$$

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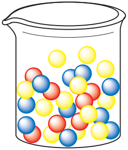
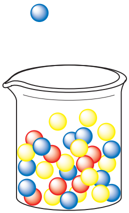


$$N_2 = n_T + n_H + n_E$$

Transition Probabilities

$$T + R_F \xrightarrow{\alpha} R_T + E$$



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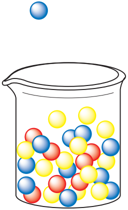

$$N_2 = n_T + n_H + n_E$$

$$\frac{n_T}{N_2}$$

Transition Probabilities

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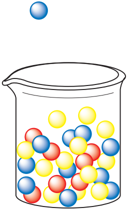

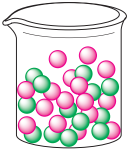

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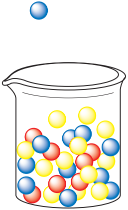

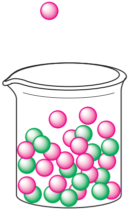

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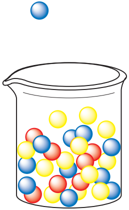

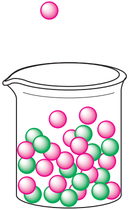

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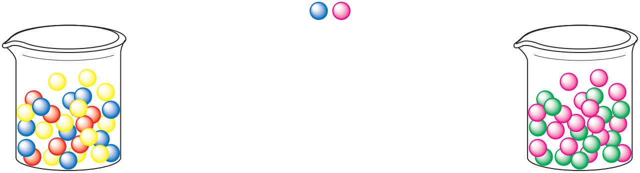

$$\frac{n_T}{N_2} \times \frac{n_{R_F}}{N_1}$$

Transition Probabilities

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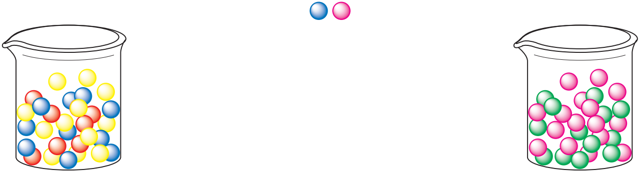

$$\alpha \quad \times \quad \frac{n_T}{N_2} \quad \times \quad \frac{n_{R_F}}{N_1}$$

The Master equation

$$\underline{n}' = \begin{cases} (n_T - 1, n_{R_T} + 1, n_H) \\ (n_T + 1, n_{R_T} - 1, n_H) \\ (n_T - 1, n_{R_T}, n_H + 1) \\ (n_T + 1, n_{R_T}, n_H) \\ (n_T, n_{R_T}, n_H + 1) \\ (n_T, n_{R_T}, n_H - 1) \end{cases}$$

$$\frac{\mathrm{d}}{\mathrm{d}t} P(\underline{n}, t) = \sum_{\underline{n}' \neq \underline{n}} T(\underline{n}|\underline{n}') P(\underline{n}', t) - \sum_{\underline{n}' \neq \underline{n}} T(\underline{n}'|\underline{n}) P(\underline{n}, t)$$

$$
\begin{aligned}
\frac{n_T}{N_2} &= \phi_T(t) + \frac{1}{\sqrt{N_2}}\xi_T \\
\frac{n_{R_T}}{N_1} &= \phi_{R_T}(t) + \frac{1}{\sqrt{N_1}}\xi_{R_T} \\
\frac{n_H}{N_2} &= \phi_H(t) + \frac{1}{\sqrt{N_2}}\xi_H
\end{aligned}
$$

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Deterministic variables

$$\frac{n_T}{N_2} = \phi_T(t) + \frac{1}{\sqrt{N_2}}\xi_T$$

$$\frac{n_{R_T}}{N_1} = \phi_{R_T}(t) + \frac{1}{\sqrt{N_1}}\xi_{R_T}$$

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Deterministic variables

Stochastic variables

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$$\frac{n_H}{N_2} = \phi_H(t) + \frac{1}{\sqrt{N_2}}\xi_H$$

Deterministic variables

Stochastic variables

System–size expansion through van Kampen theory

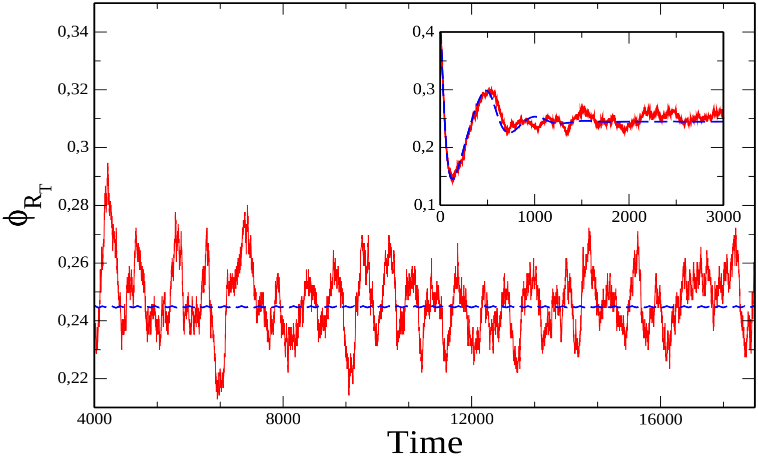
The Mean–Field System

Order $\frac{1}{\sqrt{N_1}}$ and $\frac{1}{\sqrt{N_2}}$

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}\tau}\phi_T = & - \alpha\phi_T(1-\phi_{R_T}) + \beta\phi_{R_T}(1-\phi_T-\phi_H) - (\gamma+\sigma)\phi_H\phi_T \\
& - \delta_1\phi_T + \eta_1(1-\phi_T-\phi_H) \\
\frac{\mathrm{d}}{\mathrm{d}\tau}\phi_{R_T} = & + c\left[\alpha\phi_T(1-\phi_{R_T}) - \beta\phi_{R_T}(1-\phi_T-\phi_H)\right] \\
\frac{\mathrm{d}}{\mathrm{d}\tau}\phi_H = & + \gamma\phi_H\phi_T + \eta_2(1-\phi_T-\phi_H) - \delta_2\phi_H
\end{aligned}
$$

where $c = \frac{N_2}{N_1}$ and $\tau = \frac{t}{N_2}$

Simulations



The next–to–leading order

Fokker Planck equation (FPE)

$$\frac{\partial \Pi}{\partial \tau} = -\sum_i \frac{\partial}{\partial \xi_i}\left(A(\underline{\xi})\Pi\right) + \frac{1}{2}\sum_{ij} B_{ij}\frac{\partial^2 \Pi}{\partial \xi_i \partial \xi_j}$$

$$P(\underline{n}, t) \rightarrow \Pi(\underline{\xi}, \tau)$$

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$$P(\underline{n}, t) \rightarrow \Pi(\underline{\xi}, \tau)$$

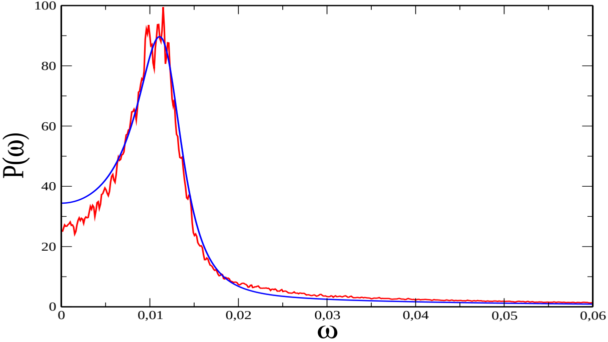
The FPE is equivalent to a set of **Langevin equations**:

$$\frac{d\xi_i}{d\tau} = A_i(\underline{\xi}) + \eta_i(\tau)$$

where $\langle \eta_i(\tau)\eta_j(\tau')\rangle = B_{ij}\delta(\tau - \tau')$

Power Spectrum

$$P_i(\omega) = \sum_j \sum_k \Phi_{ij}^{-1}(\omega) B_{jk} (\Phi_{ij}^{\dagger})^{-1}(\omega)$$



Conclusions

- **Oscillations** in pain perception and in correlated markers are found in patients under a pharmacological treatment
- A stochastic model is introduced to shed light onto the molecular mechanisms responsible for the observed behavior
- Results of simulations (supported by analytical investigation) suggest that the **intrinsic stochastic noise** could play a crucial role
- The mechanism here described is rather general and can be possibly applied to other contexts where ligand–receptor interactions do occur

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